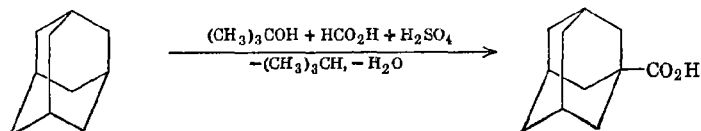


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1-ADAMANTANECARBOXYLIC ACID



Submitted by H. KOCH and W. HAAF¹

Checked by W. W. PRICHARD and B. C. MCKUSICK

1. Procedure

Caution! Because carbon monoxide is evolved, the reaction should be carried out in a good hood.

A 1-l. three-necked flask equipped with stirrer, thermometer, dropping funnel, and gas-outlet tube is charged with 470 g. (255 ml., 4.8 moles) of 96% sulfuric acid (Note 1), 100 ml. of carbon tetrachloride (Note 2), and 13.6 g. (0.100 mole) of adamantane.² The well-stirred mixture is cooled to 17–19° in an ice bath, and 1 ml. of 98% formic acid is added. Then a solution of 29.6 g. (38 ml., 0.40 mole) of *t*-butyl alcohol in 55 g. (1.2 moles) of 98–100% formic acid is added dropwise; the rate of addition and the cooling are regulated so that the addition requires 1–2 hours, and the temperature of the reaction mixture is kept at 17–25°. The reaction mixture is stirred for an additional 30 minutes and poured onto 700 g. of crushed ice. The layers are separated, and the upper, acid layer is extracted with three 100-ml. portions of carbon tetrachloride.

The combined carbon tetrachloride layers are shaken with 110 ml. of 15*N* ammonium hydroxide (Note 3), and the crystalline ammonium 1-adamantanecarboxylate that separates is collected on a Büchner funnel having a coarse fritted disk. The salt is washed with 20 ml. of cold acetone and suspended in 250 ml. of water. The suspension is made strongly acidic with 25 ml. of 12*N* hydrochloric acid and extracted with 100 ml. of chloroform. The chloroform layer is dried over anhydrous sodium sulfate and

evaporated to dryness on a steam bath (Note 4). The residue is crude 1-adamantanecarboxylic acid; weight 12–13 g. (67–72%) (Note 5); m.p. 173–174°. Recrystallization of this product from a mixture of 30 ml. of methanol and about 10 ml. of water gives 10–11 g. (56–61%) of pure acid, m.p. 175–176.5° (Note 6).

2. Notes

1. Acid concentrations of 95–98% are satisfactory. The yield falls with concentrations lower than 95%.

2. Cyclohexane or *n*-hexane can be used in place of carbon tetrachloride. Technical "normal hexane" may contain substantial amounts of methylcyclopentane and isohexane that lower the yield through formation of C₇-acids that are hard to remove.

3. A large amount of trimethylacetic acid and a small amount of at least one C₉-acid and one C₁₃-acid are formed from the *t*-butyl alcohol. The treatment with ammonia separates 1-adamantanecarboxylic acid from these acids, the ammonium salts of which remain in solution.

4. Acid that is satisfactory for most purposes may be obtained by interrupting the evaporation of the chloroform solution when crystals start to appear, cooling the concentrated chloroform solution to 0–5°, and collecting the acid on a Büchner funnel. The acid melts at 173–174°.

5. The checkers obtained similar yields when the quantity of reactants was increased fivefold.

6. As an alternative purification procedure, the checkers have esterified the crude acid by refluxing it for 2 hours with three times its weight of methanol and 2 ml. of 98% sulfuric acid. The solution is poured into 10 volumes of water and extracted with the minimum amount of chloroform required to give a clean separation of layers. The chloroform solution is washed with water, dried over calcium chloride, and distilled from a Claisen flask with an indented neck. Methyl 1-adamantanecarboxylate is collected at 77–79° (1 mm.); m.p. 38–39°. Hydrolysis of the ester with the calculated amount of 1*N* potassium hydroxide followed by acidification yields 1-adamantanecarboxylic acid; m.p. 175–176.5°; 90% overall recovery.

3. Methods of Preparation

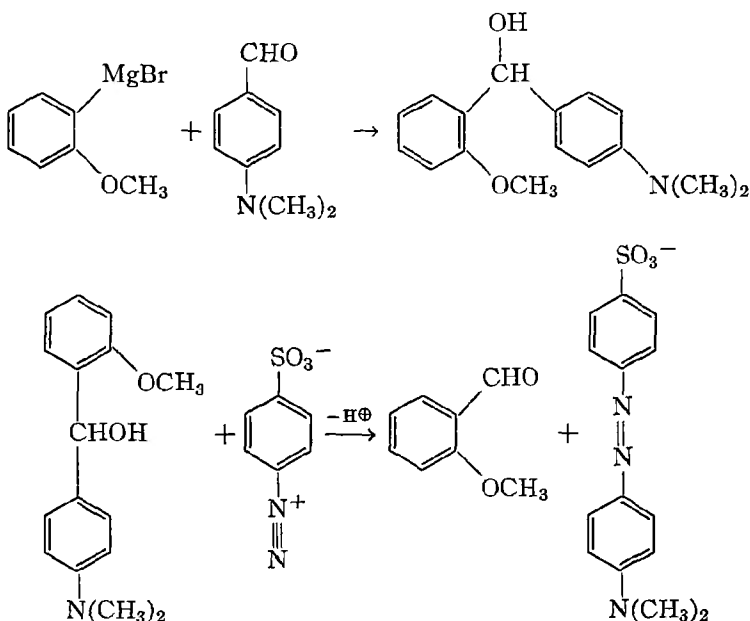
1-Adamantanecarboxylic acid can be prepared by carboxylation of 1-adamantanol³ or 1-bromoadamantane^{3,4} by formic acid and 96% sulfuric acid; by carboxylation of adamantane by formic acid, *t*-butyl alcohol, and 96% sulfuric acid;⁵ and by carboxylation of adamantane by formic acid and 130% sulfuric acid.⁶

4. Merits of the Preparation

This procedure illustrates a general method of carboxylating saturated hydrocarbons that have a tertiary hydrogen.⁷ It has been used to convert isopentane to 2,2-dimethylbutanoic acid, 2,3-dimethylbutane to 2,2,3-trimethylbutanoic acid, and methylcyclohexane to 1-methylcyclohexanecarboxylic acid.

1-Adamantanecarboxylic acid has been used to prepare many other derivatives of adamantane.⁸

1. Max-Planck Institute für Kohlenforschung, Mülheim-Ruhr, Germany.
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***o*-ANISALDEHYDE**Submitted by A. J. SISTI¹

Checked by G. L. WALFORD and PETER YATES

1. Procedure

A. 4-Dimethylamino-2'-methoxybenzhydrol. An ethereal solution of *o*-methoxyphenylmagnesium bromide is prepared in the usual manner² with 250 ml. of anhydrous ether, 14.5 g. (0.60 g. atom) of magnesium, and 100 g. (0.53 mole) of *o*-bromoanisole (Note 1). A solution of 60 g. (0.40 mole) of *p*-dimethylaminobenzaldehyde (Note 2) in 200 ml. of anhydrous benzene is added dropwise to the Grignard reagent (Note 3). After the addition is completed, the reaction mixture is stirred for 10 hours at room

temperature. The magnesium complex, which forms a very thick suspension, is decomposed with a solution of 75 g. of ammonium chloride in 450 ml. of water. The ether-benzene layer is separated, washed with 100 ml. of water, and dried over calcium sulfate (Note 4). The solvent is removed under reduced pressure, and the residue is induced to crystallize by trituration with a little petroleum ether (30–60°). Recrystallization of the solid from benzene-petroleum ether (30–60°) gives 4-dimethylamino-2'-methoxybenzhydrol (59–60 g., 57–58%), m.p. 75–80°.

B. *o*-Anisaldehyde. In a 3-l. three-necked flask fitted with a mechanical stirrer and a nitrogen inlet tube are placed 60 g. (0.35 mole) of sulfanilic acid (Note 5), 18 g. (0.17 mole) of anhydrous sodium carbonate, and 400 ml. of water. Stirring is started, and the resulting solution is cooled to 0–5° in an ice bath. Nitrogen is passed into the reaction flask, and a nitrogen atmosphere is maintained throughout the reaction. To the cooled solution is added three-quarters of a solution of 24.2 g. (0.35 mole) of sodium nitrite in 75 ml. of water, followed by 32 ml. of concentrated hydrochloric acid. During the diazotization the temperature of the solution is maintained below 5° by the addition of ice in small pieces. After a few minutes another 32 ml. of acid is added. Further additions of the sodium nitrite solution are made slowly until a positive test for excess nitrous acid is observed (Note 6). The diazonium solution is buffered to pH ~6 by the addition of a cooled solution of 50 g. of sodium acetate in 125 ml. of water. A solution of 52 g. (0.20 mole) of 4-dimethylamino-2'-methoxybenzhydrol in 500 ml. of acetone is added rapidly, followed by an additional 500 ml. of acetone. The reaction mixture becomes red almost immediately, and stirring is continued for 30 minutes at 0–5°. The cooling bath is replaced by a warm water bath (50–60°), and stirring is continued for an additional 30 minutes. The reaction mixture is diluted with an equal volume of water and extracted with three 750-ml. portions of ether. The combined ethereal extracts are washed with water until all the dissolved methyl orange is removed, then dried over calcium sulfate. The ether is removed under reduced pressure, and the residue is distilled to yield 19–20.5 g. (69–75%) of colorless liquid, b.p. 79–80° (1.5 mm.), n_D^{25} 1.5586 (Note 7).

2. Notes

1. *o*-Bromoanisole obtained from Eastman Kodak Company was used without further purification.

2. A good commercial grade (Matheson, Coleman and Bell) of *p*-dimethylaminobenzaldehyde was used without further purification.

3. In one run the checkers cooled the reaction mixture in an ice bath throughout the addition. In another run only initial cooling was used. There was no difference in yield.

4. The checkers found that separation of the aqueous and organic phases is very difficult if the mixture is shaken. In one run shaking and washing were omitted without affecting the yield or purity of the product.

5. Eastman white label sulfanilic acid was used without purification.

6. Excess nitrous acid causes an *immediate* blue color at the point of contact with starch-iodide test paper. At all times there must be an excess of mineral acid (Congo red test paper).

7. The submitters found for the 2,4-dinitrophenylhydrazone m.p. 252–254° (lit.² m.p. 249–250°). The checkers found m.p. 34–36° for *o*-anisaldehyde (lit.³ m.p. 37°) and m.p. 249–251° for the 2,4-dinitrophenylhydrazone.

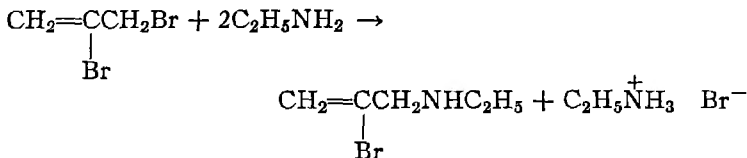
3. Methods and Merits of Preparation

o-Anisaldehyde is commercially available. However, this procedure illustrates a method of general applicability^{4,5} for the preparation of aromatic, aliphatic, and unsaturated aldehydes.

1. Department of Chemistry, Adelphi College, Garden City, Long Island, New York.
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4. M. Stiles and A. J. Sisti, *J. Org. Chem.*, **25**, 1691 (1960).
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N-(2-BROMOALLYL)ETHYLAMINE

(Allylamine, 2-bromo-N-ethyl-)

Submitted by ALBERT T. BOTTINI and ROBERT E. OLSEN¹

Checked by THOMAS H. LOWRY and E. J. COREY

1. Procedure

Caution! This preparation should be carried out in a hood to avoid exposure to ethylamine, 2,3-dibromopropene, and the product. 2,3-Dibromopropene is a strong lachrymator. The operator should wear rubber gloves and protective goggles because some 2-haloallyl amines have caused severe skin and eye irritation.

A 1-l. three-necked flask is fitted with a sealed mechanical stirrer, a dropping funnel, and a dry ice condenser charged with an ice-salt mixture (Note 1). Three hundred milliliters (240 g., 3.7 moles) of aqueous 70% ethylamine solution (Note 2) is placed in the flask, the stirrer is started, and 200 g. (1.00 mole) of 2,3-dibromopropene (Note 3) is added dropwise over a period of 1 hour. After the addition is complete, the reaction mixture is stirred for 3 hours. Ether (300 ml.) is added, and the mixture is cooled in an ice bath. Sodium hydroxide (100 g.) is added with stirring and cooling. The cold mixture is transferred to a separatory funnel, and the phases are separated. The organic layer is dried in two stages over 25-g. portions of sodium hydroxide. The organic layer and the small amount of water that separates during the second stage of drying are decanted into a separatory funnel, and the phases are separated. Most of the ether and unreacted ethylamine are removed from the organic layer by distillation through a 250-mm. x 13-mm. column packed with glass helices, and the residue is distilled through the same column at

reduced pressure under nitrogen to give 115–128 g. (70–78%) of N-(2-bromoallyl)ethylamine; b.p. 53–55° (27 mm.), 79–81° (75 mm.) (Note 4); n_D^{25} 1.4765–1.4770.

2. Notes

1. The checkers used an inner-spiral water condenser. The cooling water was chilled to about 0° by prior passage through a short copper coil immersed in ice.

2. The aqueous 70% ethylamine solution used was the practical grade obtained from Eastman Organic Chemicals.

3. The 2,3-dibromopropene used was obtained from Columbia Organic Chemicals Co., Columbia, South Carolina, and was redistilled before use. The preparation of 2,3-dibromopropene is described in an earlier volume of this series.²

4. The reported boiling point of N-(2-bromoallyl)ethylamine is 148–153°.⁴ It is strongly recommended that the product and other 2-haloallylamines be distilled at reduced pressure under nitrogen, for the submitters have noted two instances when a 2-haloallylamine polymerized with considerable evolution of heat during slow distillation at atmospheric pressure.

3. Methods of Preparation

This method is essentially that described by Pollard and Parcell.³ No other procedure appears to have been used to prepare N-(2-bromoallyl)ethylamine. A number of N-(2-haloallyl)alkylamines have been prepared by treatment of a 2,3-dihalopropene with a primary alkylamine in water,^{3,4} ether,^{3,4} or benzene.⁵

4. Merits of the Preparation

The method described here has been used for the preparation of a number of N-(2-haloallyl)alkylamines from a water-soluble amine and the corresponding 2,3-dihalopropene.^{3,4}

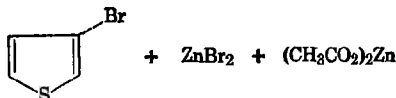
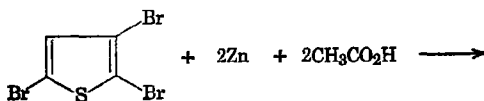
Treatment of an N-(2-bromoallyl)alkylamine with sodium amide in liquid ammonia yields the N-alkylallenimine together with a small amount of the N-alkylpropargylamine.³⁻⁷ Similar

treatment of an N-(2-chloroallyl)alkylamine yields only the N-alkylpropargylamine.^{4,6}

1. Department of Chemistry, University of California, Davis, California.
2. R. Lespieau and M. Bourguet, *Org. Syntheses*, Coll. Vol. 1, 209 (1941).
3. C. B. Pollard and R. F. Parcell, *J. Am. Chem. Soc.*, **73**, 2925 (1951).
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3-BROMOTHIOPHENE

(Thiophene, 3-bromo-)



Submitted by S. GRONOWITZ and T. RAZNIKIEWICZ¹

Checked by MAX TISHLER, ARTHUR J. ZAMBITO, and RONALD B. JOBSON

1. Procedure

A 5-l., three-necked, round-bottomed flask is equipped with an efficient stirrer (Note 1), a reflux condenser, and a dropping funnel. Water (1850 ml.) is added, stirring is begun and continued throughout the procedure, and 783 g. (12.0 moles) of zinc dust (Note 2) and 700 ml. of acetic acid are added. The mixture is heated to reflux, the heating mantle is removed, and 1283 g. (4.00 moles) of 2,3,5-tribromothiophene (Note 3) is added dropwise at such a rate that the mixture continues to reflux. The addition is complete in about 70 minutes. Heat is applied, and the mixture is refluxed for 3 hours. A condenser is arranged for downward distillation, and the mixture is distilled until no more or-

ganic substance distills with the water (Note 4). The heavier organic layer is separated, washed successively with 50 ml. of 10% sodium carbonate solution and 100 ml. of water, dried over calcium chloride (Note 5), and fractionated through a vacuum-mantled Dufton column (Note 6). A 19-g. fore-run, b.p. 78–159°, consists mainly of thiophene and 3-bromothiophene. 3-Bromothiophene is collected at 159–160°; n_{D}^{20} 1.5919–1.5928; weight 580–585 g. (89–90%) (Notes 7 and 8).

2. Notes

1. The submitters used a Teflon® paddle-type stirrer sealed with rubber tubing lubricated by glycerol and driven by a powerful motor. The checkers used a Trubore® stirrer.

2. Mallinckrodt zinc powder (analytical reagent grade) is used.

3. 2,3,5-Tribromothiophene is conveniently prepared by the method of Troyanowsky.² Thiophene (1125 g., 13.4 moles) and 450 ml. of chloroform are charged into a 5-l. three-necked flask equipped with a stirrer, a dropping funnel, and an outlet for the hydrogen bromide evolved. The flask is in a deep pan through which cold tap water passes. Bromine (6480 g., 40.6 moles) is added dropwise to the stirred mixture over a period of 10 hours. After the mixture has stood overnight, it is heated at 50° for several hours, washed with 2*N* sodium hydroxide solution, refluxed for 7 hours with a solution of 800 g. of potassium hydroxide in 1.5 l. of 95% ethanol, and poured into water. The organic layer is separated, washed with water, dried over calcium chloride, and fractionated to give 3200–3650 g. (75–85%) of 2,3,5-tribromothiophene; b.p. 123–124° (9 mm.); m.p. 25–27°.

4. About half of the volume is distilled over. The temperature of the vapor rises during the distillation from 95° to 101°.

5. The checkers washed the drying agent with ether and combined the wash with the filtrate.

6. A Dufton column was not available to the checkers. In its place a 2.5-cm. x 38-cm. column packed with glass helices was used. This column was heated by a 4.5-cm. concentric glass jacket wrapped with Nichrome ribbon. A 6.5-cm. concentric

glass jacket surrounded the whole column and served to insulate it.

7. In several experiments on one-fifth the scale, the yields were 89–92%.

8. Infrared analysis shows that the 3-bromothiophene contains about 0.5% of 2-bromothiophene, as measured by 2-bromothiophene's characteristic absorption peak at $10.26\ \mu$. The traces of this lower-boiling isomer can easily be removed by fractionation through a more efficient column.

3. Methods of Preparation

The procedure described is a modification of that described by Gronowitz.³ 3-Bromothiophene has been obtained more tediously and in lower yields by removal of the α -bromines of 2,3,5-tribromothiophene through the Grignard entrainment method⁴ with ethyl bromide as the auxiliary halide, or by halogen-metal interconversion with *n*-butyllithium⁵ followed by hydrolysis of the organometallic compounds. It has also been obtained from 4,5-dibromo-2-thiophenecarboxylic acid through simultaneous debromination and decarboxylation.⁶

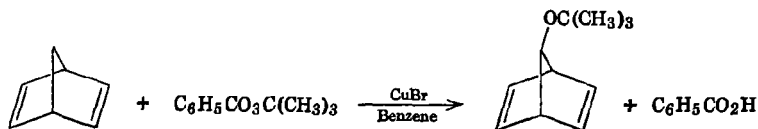
4. Merits of the Preparation

3-Bromothiophene is a key intermediate for the synthesis of 3-substituted thiophenes.⁷

1. Department of Organic Chemistry, Chemical Institute, University of Uppsala, Sweden.
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7-*t*-BUTOXYNORBORNADIENE

(2,5-Norbornadiene, 7-*tert*-butoxy-)



Submitted by PAUL R. STORY and SUSAN R. FAHRENHOLTZ¹

Checked by ERIC BLOCK and E. J. COREY

1. Procedure

A 2-l. three-necked flask, fitted with stirrer, condenser, dropping funnel, and an arrangement for maintenance of an inert atmosphere, is charged with a mixture of 300 g. (3.26 moles) of norbornadiene (Note 1) and 0.650 g. (4.53 mmoles) of cuprous bromide (Note 2) in 500 ml. of benzene (Note 3). Dry nitrogen is introduced continuously, and, after the flask contents are brought to reflux, 245 g. (1.26 mole) of *t*-butyl perbenzoate (Note 4), dissolved in 100 ml. of benzene, is added over approximately 1 hour to the stirred mixture. The solution immediately becomes blue or blue-green. The modest heat of reaction requires the application of some heat throughout the reaction period in order to maintain reflux. After the addition is completed, the solution is heated at the reflux temperature for an additional 30 minutes (*Caution!* Note 5).

The mixture is cooled to room temperature, transferred to a 4-l. separatory funnel, and washed with three 300-ml. portions of saturated brine, to remove copper salts, and three 300-ml. portions of 10% aqueous sodium hydroxide, to remove benzoic acid (Note 6). The benzene solution is then washed with 150 ml. of brine and is dried over anhydrous sodium sulfate.

The dried solution is transferred to a 2-l. flask fitted with a Claisen head attached to a 30-cm. Vigreux column. Benzene is

removed fairly rapidly at about 200 mm. so that the benzene boils at 45–50° (Note 7). After removal of most of the benzene, the pressure is slowly lowered to 10–15 mm.; a negligible amount of fore-run is obtained before the product begins to distil at about 65° at 15 mm. The product is collected until the temperature reaches 80–85° at the same pressure (Note 8). The yield of 7-*t*-butoxynorbornadiene is 42–51 g. (20–25%, based on *t*-butyl perbenzoate) (Note 9). Gas-phase chromatographic analysis of the product shows it to be about 95% pure. Greater purity can be obtained, if required, by fractionation through a spinning band column; the pure product is collected at 70–72° (14 mm.) (Note 10).

2. Notes

1. Norbornadiene as supplied by Shell Chemical Co. is used without further purification. Distillation of the norbornadiene immediately before use gives no change in yield of 7-*t*-butoxynorbornadiene.

2. The cuprous bromide was used as obtained from E. H. Sargent Co. One instance of an ineffective batch of cuprous bromide from another source has been reported to the submitters. Cuprous bromide is only slightly soluble in the benzene solution. Greater amounts of catalyst have no effect on the yield of product.

3. Baker and Adamson or Merck reagent grade benzene was used.

4. *t*-Butyl perbenzoate was used as received from Lucidol Division of Wallace and Tiernan Co., Buffalo, New York.

5. Normally, after this time, the *t*-butyl perbenzoate is completely reacted. It is advisable, however, to check for its presence because distillation of a crude product containing some perester can lead to an explosion. *t*-Butyl perbenzoate absorbs strongly in the infrared at 5.65–5.70 μ , and examination of the infrared spectrum of the benzene solution is a sufficiently sensitive test. No difficulty has ever been encountered during reactions with norbornadiene. However, unreacted *t*-butyl perbenzoate has caused a minor explosion with another, less reactive olefin.

6. Unless the copper salts are removed first, the basic wash frequently produces a thick emulsion which requires considerable time to settle.

7. The benzene is removed at reduced pressure to minimize heating of the product which consists chiefly of high-boiling esters. The last trace of benzene and norbornadiene is removed at a lower pressure.

8. 7-*t*-Butoxynorbornadiene is collected over this wide temperature range since the last portion of the distillate is superheated because of the large quantity of high-boiling materials remaining in the pot. No other reaction products boil in the same range, and GPC analysis has shown the last fraction of distillate to be nearly as pure as the middle cut.

9. This reaction has been conducted under a variety of conditions, but the yield of 7-*t*-butoxynorbornadiene has never been less than 20% or greater than 26%.

10. Infrared (μ , CCl_4): 6.48 (w), 7.20 (m), 7.35 (s), 7.61 (m), 9.05 (s), 13.7 (s). The absorptions at 6.48 (double-bond stretch) and 13.7 (*cis* double bond C—H out-of-plane deformation) are very characteristic of the norbornadiene nucleus. N.m.r. spectrum (CCl_4): τ = 3.56 (m), 3.70 (m), 6.77 (m), 6.38 (m), 8.94 (s).

3. Methods of Preparation

The only method reported² for the preparation of 7-*t*-butoxynorbornadiene is that described here. The general reaction of *t*-butyl perbenzoate with various olefins has been described by many investigators.³ When benzoyl peroxide is used in place of *t*-butyl perbenzoate under similar conditions, 7-benzoxynorbornadiene is obtained in 38% yield; it is said to be more easily hydrolyzed to the alcohol than 7-*t*-butoxynorbornadiene.⁴

4. Merits of the Preparation

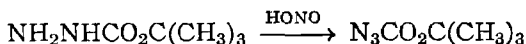
7-*t*-Butoxynorbornadiene provides a convenient route to 7-substituted norbornenes and norbornadienes including *anti*-7-norbornenol,² 7-norbornadienyl acetate,² 7-norbornadienol,² 7-chloronorbornadiene,⁵ 7-methylnorbornadiene,⁶ and 7-phenylnorbor-

nadiene.⁶ These compounds are useful in studies of the nature of chemical bonding.^{5,7}

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t-BUTYL AZIDOFORMATE

(Formic acid, azido-, *tert*-butyl ester)



Submitted by LOUIS A. CARPINO, BARBARA A. CARPINO,
PAUL J. CROWLEY, CHESTER A. GIZA,
and PAUL H. TERRY¹

Checked by VIRGIL BOEKELHEIDE and S. J. CROSS

1. Procedure

In a 1-l. round-bottomed flask fitted with a mechanical stirrer are placed 82 g. (0.62 mole) of *t*-butyl carbazate,² 72 g. of glacial acetic acid, and 100 ml. of water. The solution is cooled in an ice bath, and 47.0 g. (0.68 mole) of solid sodium nitrite is added over a period of 40–50 minutes, the temperature being kept at 10–15° (Note 1). The mixture is allowed to stand in the ice bath for 30 minutes, 100 ml. of water is added, and the floating oil is extracted into four 40-ml. portions of ether. The combined ether extracts are washed twice with 50-ml. portions of water and with 40-ml. portions of 1*M* sodium bicarbonate solution until no longer acidic (about three washings are required). The solution is dried over magnesium sulfate, and the ether is removed by distillation from a water bath maintained at 40–45°; water aspirator pressure of 140–150 mm. is used. The pressure is then

lowered to 70 mm., and the water bath temperature is raised to 90–95°. The azide is distilled (*Caution! Note 2*) using a Claisen flask and is collected at 73–74° (70 mm.), n_D^{24} 1.4227, after a few drops of fore-run. The yield is 57–72.8 g. (64–82%) (Notes 3 and 4).

2. Notes

1. The sodium nitrite may be added as a concentrated aqueous solution.

2. It is recommended that the distillation be carried out behind a safety shield. The submitters have distilled this compound several hundred times without incident under the conditions given on a scale up to 300–400 g. per run. On the other hand, Prof. P. G. Katsoyannis (University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania) has reported that an explosion took place in the receiving flask while the compound was being distilled under conditions previously used without incident. The reason for the explosion could not be traced. According to Prof. R. Schwyzer (Ciba, Ltd., Basel, Switzerland) tests at a Swiss Federal Institute showed that the compound could not be exploded by mere heating: it simply decomposes. For explosion, one must apply a primary explosive such as lead azide or silver azide. An attempt by the submitters to distil the azide at atmospheric pressure resulted in vigorous carbonization, but no explosion occurred. In view of the potential hazard some investigators prefer not to distil the azide; they use the crude material after removal of solvent. High yields of carbo-*t*-butoxy derivatives may be obtained in this way.

3. When freshly distilled, the azide is water-white. When the azide is allowed to stand for several weeks, it slowly develops a light yellow color; however, this does not appear to affect its reactivity as an acylating agent.¹

4. The azide should be handled with adequate ventilation. Careless inhalation of the substance was accompanied by development of a painful throbbing headache or a sensation of giddiness or both. These effects disappeared within several hours upon exposure to fresh air.

3. Methods of Preparation

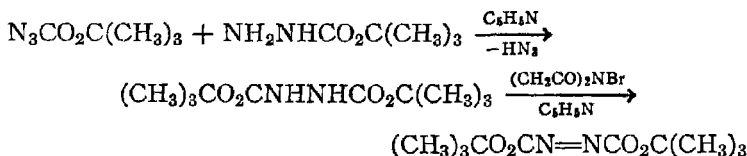
t-Butyl azidoformate has been prepared only from *t*-butyl carbazate.³⁻⁶

4. Merits of the Preparation

t-Butyl azidoformate serves as a convenient reagent for the acylation of amines, hydrazines, and similar compounds.³ The instability of *t*-butyl chloroformate makes *t*-butyl azidoformate the reagent of choice for introducing the carbo-*t*-butoxy group. In view of the recent work on the generation of nitrenes from azidoformates and their conversion to azepines,^{6,7} it would appear that *t*-butyl azidoformate should be a useful reagent in this regard as well.

The acylation product of hydroxylamine, *t*-butyl N-hydroxycarbamate,⁵ is a valuable intermediate in the synthesis of O-substituted hydroxylamines such as O-acyl- and O-sulfonylhydroxylamines, many of which are valuable aminating agents and have not been obtained in any other way.^{8,9}

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***t*-BUTYL AZODIFORMATE**(Formic acid, azodi-, di-*tert*-butyl ester)Submitted by LOUIS A. CARPINO and PAUL J. CROWLEY¹

Checked by VIRGIL BOEKELHEIDE and S. J. CROSS

1. Procedure

A. *t*-Butyl hydrazodiformate. A solution of 28.6 g. (0.2 mole) of *t*-butyl azidoformate² and 26.4 g. (0.2 mole) of *t*-butyl carbazate³ in 60 ml. of pyridine (Note 1) is allowed to stand at room temperature for 1 week and is then diluted with 500 ml. of water. The snow-white microcrystalline powder that separates is removed by filtration and is washed with two 50-ml. portions of water. The yield of air-dried hydrazide, m.p. 124–126°, is 35.5–37 g. (77–80%).⁴ The product is pure enough for most applications but may be purified by recrystallization from a 1:1 mixture of benzene and ligroin (60–90°) from which it separates as small white needles, m.p. 124–125.5°. The recovery is 92%.

B. *t*-Butyl azodiformate. In a 500-ml. Erlenmeyer flask is placed a solution of 23.2 g. (0.1 mole) of crude *t*-butyl hydrazodiformate (m.p. 124–126°) in 175 ml. of methylene chloride and 7.9 g. (0.1 mole) of pyridine (Note 1). The solution is cooled by a stream of running tap water while 18.2 g. (0.102 mole) (Note 2) of N-bromosuccinimide (Note 1) is added during 6–7 minutes with swirling. The resulting solution is allowed to stand at room temperature for 5 minutes and is washed with two 100-ml. portions of water followed by one 100-ml. portion of 10% sodium hydroxide. The solution is dried for 30 minutes over magnesium sulfate, filtered into a large evaporating dish, and allowed to

evaporate. The yellow-orange crystalline residue, m.p. 90–91.5°, which amounts to 20.7–21.8 g. (90–94.5%), is recrystallized by covering the dry solid with 35–40 ml. of petroleum ether (b.p. 30–60°) and adding ligroin (b.p. 60–90°) to the boiling solution until the solid dissolves. *t*-Butyl azodiformate, 19.8–20.0 g., m.p. 90.7–92°, separates from the cooled solution as large lemon-yellow crystals. Evaporation of the filtrate gives an additional amount of yellow solid which is recrystallized as before, yielding 0.4–0.7 g. of pure material, m.p. 90–92°. The total yield is 20.2–20.7 g. (88–90%).

2. Notes

1. The pyridine was a pure product, b.p. 113–115°, obtained from Mallinckrodt Chemical Company and used as supplied. The methylene chloride (technical grade) and N-bromosuccinimide (practical grade) were obtained from the Matheson Company and used as received.

2. Unless a 2% excess of N-bromosuccinimide is used, the azo compound is contaminated by an impurity, possibly the original hydrazo compound, which separates along with the desired product in the form of long, easily distinguished needles. The two substances cannot be separated by crystallization from ligroin.

3. Methods of Preparation

t-Butyl hydrazodiformate has been prepared by acylation of *t*-butyl carbazate by means of *t*-butyl azidoformate⁴ or *t*-butyl cyanoformate.⁵ *t*-Butyl azodiformate has been prepared only by oxidation of the hydrazo compound.⁶

4. Merits of the Preparation

The potassium salt of *t*-butyl hydrazodiformate can be easily alkylated and thus used in the synthesis of acyclic and cyclic 1,2-disubstituted hydrazines.⁷

Ethyl azodiformate is a well-known and useful dienophile in the Diels-Alder reaction.⁸ *t*-Butyl azodiformate behaves simi-

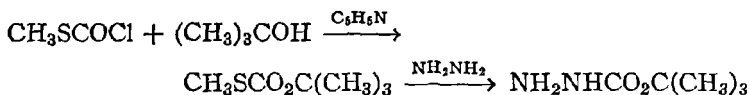
larly, although it is somewhat less reactive.⁶ *t*-Butyl azodiformate does, however, provide products with ester groups that are easily cleaved. Monosubstituted hydrazines may be prepared by the addition of Grignard reagents to azoformates followed by cleavage.⁶

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***t*-BUTYL CARBAZATE**

(Carbamic acid, *tert*-butyl ester)

Method I



Submitted by LOUIS A. CARPINO, DAVID COLLINS, SIEGFRIED GÖWECKE,
JOE MAYO, S. D. THATTE, and FRED TIBBETTS¹

Checked by FRED G. H. LEE and VIRGIL BOEKELBEIDE

1. Procedure

Caution! Methyl chlorothiolformate has an obnoxious odor. All operations should be conducted in a well-ventilated hood.

A. *t*-Butyl *S*-methylthiolcarbonate. In a 5-l. round-bottomed flask, fitted with mechanical stirrer, reflux condenser, and dropping funnel are placed 430 ml. (422 g., 5.33 moles) of pyridine, 508 ml. (395 g., 5.33 moles) of *t*-butyl alcohol, and 1.6 l. of chloro-

form (Note 1). The solution is stirred while 536 g. (4.85 moles) of methyl chlorothiolformate (Note 2) is added dropwise over a period of 30–40 minutes, and the solution is then stirred and heated at the reflux temperature for 24 hours. The resulting solution is divided into three equal portions of about 1 l., and each portion is washed in a 2-l. separatory funnel with two 500-ml. portions of water, three 275-ml. portions of 5% hydrochloric acid, and finally with 350 ml. of 1*M* sodium bicarbonate solution. The combined chloroform solutions are dried over anhydrous magnesium sulfate for 5 hours, and the solvent is removed by distillation from a water bath at atmospheric pressure followed by the use of a water aspirator. Distillation (Note 3) of the residue from a 1-l. Claisen flask by means of a water or oil bath gives 419–497 g. (58–69%) of a colorless liquid, b.p. 62–65° (24 mm.), n_D^{25} 1.4525. This product is sufficiently pure for use in the preparation below but may be purified by distillation through a 30-cm. helices-packed column which gives 375–447 g. (52–62%) of the ester, b.p. 60–63° (24 mm.).

B. *t*-Butyl carbazate. In a 2-l. round-bottomed flask set up in a hood and fitted with an efficient mechanical stirrer and a reflux condenser are placed 500 g. (3.47 moles) of *t*-butyl S-methylthiolcarbonate and 186 g. (3.71 moles) of 64% hydrazine solution (Note 4). The contents of the flask are heated in an oil bath at 105–110° (external temperature) with mechanical stirring for 24 hours under a reflux condenser. The resulting mixture is diluted with 650 ml. of methylene dichloride, and anhydrous magnesium sulfate is added until the aqueous layer becomes nearly solid and nonflowing. The upper layer is decanted and dried over fresh anhydrous magnesium sulfate and the solvent removed by distillation from a water bath, the last portions being removed with the aid of a water aspirator. The residual liquid solidifies on cooling and stirring to give 322–385 g. (72–86%) of a snow-white solid, m.p. 37–40°. This product is pure enough for most purposes but can be purified by distillation, a 1-l. Claisen flask with a water or oil bath at 80° being used. After 1 or 2 drops of fore-run the carbazate is collected at 55–57° (0.4 mm.). The oil solidifies on cooling to give 312–358 g. (70–80%) of snow-white crystalline solid, m.p. 40–42° (Note 5).

2. Notes

1. The pyridine was a pure product, b.p. 113–115°, obtained from the Mallinckrodt Chemical Company. *t*-Butyl alcohol, m.p. 24.5–25.5°, and chloroform (U.S.P. or reagent grade) were obtained from the Matheson Company. All reagents were used as supplied.

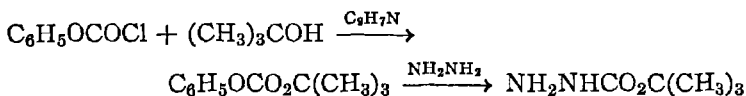
2. The methyl chlorothiolformate, b.p. 110–111°, was used as supplied by the Stauffer Chemical Company.

3. This distillation is accompanied by foaming which is very difficult to prevent. The checkers recommend carrying out the distillation in two separate batches to allow greater free space in the distillation flask.

4. Hydrazine hydrate (64% hydrazine) was used as supplied by the Fairmount Chemical Company.

5. Further purification can be effected by recrystallization with 90% recovery from a 50-50 mixture of low- (b.p. 30–60°) and high-boiling (b.p. 60–70°) ligroin. This procedure gives white needles, m.p. 41–42°.

Method II



Submitted by LOUIS A. CARPINO, BARBARA A. CARPINO, CHESTER A. GIZA,
ROBERT W. MURRAY, ARTHUR A. SANTILLI, and PAUL H. TERRY¹

Checked by VIRGIL BOECKELHEIDE and S. J. CROSS

1. Procedure

A. *t*-Butyl phenyl carbonate. In a 2-l. round-bottomed flask fitted with thermometer, dropping funnel, and mechanical stirrer are placed 248 g. (3.35 moles) of *t*-butyl alcohol, 430 g. (3.33 moles) of quinoline, and 500 ml. of methylene dichloride (Note 1). The solution is stirred while 520 g. (3.32 moles) of phenyl chloroformate (Note 2) is added dropwise over a period of 4 hours.

During the addition the temperature is maintained at 28–31° (Note 3) by cooling the flask, as needed, by a stream of tap water. The solution is allowed to stand overnight and is then treated with 800 ml. of water to dissolve the precipitated quinoline hydrochloride (Note 4). The mixture is shaken well in a separatory funnel; the organic layer is separated and washed with two 200-ml. portions of water and three or four 200-ml. portions of 5% hydrochloric acid. After the extract has dried over anhydrous magnesium sulfate for 5 hours, the solvent is removed by distillation, a water aspirator being used to remove the last portions of the methylene dichloride. Distillation of the residue from a 1-l. Claisen flask by means of an air bath maintained at 125–135° gives 460–495 g. (71–76%) (Note 5) of a colorless oil, b.p. 74–78° (0.5 mm.), n_{D}^{24} 1.4832. This product is sufficiently pure for use in the preparation below.

B. *t*-Butyl carbazate. In a 1-l. Erlenmeyer flask are placed 388.4 g. (2.0 moles) of phenyl *t*-butyl carbonate and 120.2 g. (2.4 moles) of a 64% hydrazine solution (Note 6). The mixture is swirled by hand and heated on a hot plate. When the internal temperature reaches 75–80°, it then rises rapidly and spontaneously to 104–110°, the two layers forming a clear solution. The solution is allowed to cool overnight. The mixture is then diluted with 500 ml. of ether and transferred to a separatory funnel in which it is shaken vigorously for about 10 minutes with a solution prepared from 160 g. (4.0 moles) of sodium hydroxide and 1.2 l. of water. The resulting two layers are placed in a 2-l. continuous extractor and extracted for 48 hours with ether. The ether solution is dried over magnesium sulfate, and the ether is removed by distillation from a water bath. The last portions of ether are removed with the aid of a water aspirator. The residual oil is then distilled using a Claisen flask with an air bath maintained at 115–125°. After 1 or 2 drops of fore-run the carbazate is collected at 61–65° (1.2 mm.), n_{D}^{24} 1.4518. The yield is 235–256 g. (89–97%) (Note 7).

2. Notes

1. The *t*-butyl alcohol and methylene dichloride were used directly as received from the Matheson Company. The quinoline

was a practical grade material (Eastman Kodak Company) which was redistilled [b.p. 100–102° (25 mm.)].

2. Phenyl chloroformate was prepared by the method of Strain *et al.*,² except that methylene dichloride or chloroform was used in place of benzene as the solvent. The yield was 85–95% [b.p. 74–76° (15 mm.), n_{D}^{24} 1.5125]. The checkers used commercial phenyl chloroformate (Eastman Kodak).

3. The reaction may be run without cooling by adding the acid chloride at a rate to maintain the temperature at 39–43°. On the scale indicated this requires about 5 hours. The yield is substantially the same, although more high-boiling material is formed.

4. Occasionally the quinoline hydrochloride does not separate; this does not affect the yield, however. If it is desired to recover the quinoline, the salt may be filtered at this point, dissolved in water, and converted to the free base.

5. The carbonate decomposes on attempted distillation of large amounts at water aspirator pressure (20–25 mm.).

6. Hydrazine hydrate (61% hydrazine) was used as supplied by the Olin-Mathieson Company.

7. The carbazate is sufficiently pure for most applications and is conveniently handled as a liquid. When the product is cooled in an ice box, it crystallizes as a waxy mass; such samples remain tacky after several recrystallizations from petroleum ether, however. A pure sample may be obtained by extracting an ether solution of the carbazate with dilute sodium hydroxide to remove any phenol, followed by distillation and recrystallization of the product from petroleum ether (b.p. 30–60°). White needles are obtained which melt at 41–42°.

3. Methods of Preparation

t-Butyl S-methylthiolcarbonate has been prepared from sodium *t*-butoxide, carbonyl sulfide, and methyl iodide³ and from methyl chlorothiolformate and *t*-butyl alcohol.⁴ *t*-Butyl phenyl carbonate has been prepared from phenyl chloroformate and *t*-butyl alcohol.^{5, 6}

t-Butyl carbazate has been prepared by reaction of hydrazine with *t*-butyl phenyl carbonate,^{5, 6} *t*-butyl S-methylthiolcarbonate,³

t-butyl-*p*-nitrophenyl carbonate,⁷ and N-*t*-butyloxycarbonyl-imidazole.⁸

4. Merits of the Preparation

Method I is easily adapted to larger-scale operation and provides a product which crystallizes readily. Method II provides a product which is difficult to crystallize; however, the procedure obviates the use of methyl chlorothiolformate and affords higher yields of product.

t-Butyl carbazate is a useful reagent for preparing 1,1-disubstituted hydrazines.⁶ In turn, the 1,1-disubstituted hydrazines can undergo an elimination of nitrogen followed by radical coupling of the two substituent groups. This reaction is promoted either by direct oxidation of the 1,1-disubstituted hydrazine⁹⁻¹¹ or by base-catalyzed elimination of benzenesulfinic acid from the corresponding benzenesulfonylhydrazide.⁶ For example, 1,1-dibenzyl-2-benzenesulfonylhydrazide is converted to bibenzyl in 85% yield.

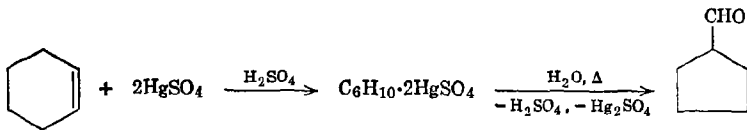
t-Butyl carbazate is also a key intermediate in the synthesis of *t*-butyl azidoformate,^{5, 6, 12} *t*-butyl hydrazodiformate,⁶ *t*-butyl azodiformate,¹³ and *t*-butyl N-hydroxycarbamate,^{12, 14} all of which are valuable synthetic intermediates.

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t*-BUTYL HYPOCHLORITE*WARNING**

It has been reported¹ that, during the preparation of *t*-butyl hypochlorite according to the directions published in this series,² an explosion occurred and caused moderate physical damage and minor injury to the operator. The cause of the accident has been attributed to lack of proper temperature control during addition of chlorine. It is strongly recommended that the reaction vessel be fitted with a thermometer that dips into the reaction mixture and that the rate of flow of chlorine be regulated so that the temperature of the reaction mixture never exceeds 20°.

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CYCLOPENTANECARBOXALDEHYDE

Submitted by OLIVER GRUMMITT, JOHN LISKA, and GERHARD GREULL¹
 Checked by WILLIAM E. PAREHAM and GERALD E. STOKKER

1. Procedure

In a 5-l. three-necked flask fitted with reflux condenser, mechanical stirrer, thermometer, and nitrogen gas inlet is placed a solution of 80.0 g. (43.5 ml., 0.82 mole) of concentrated sulfuric acid in 3 l. of water. The solution is stirred under nitrogen, and 740.0 g. (2.49 moles) of reagent mercuric sulfate is added to form a suspension of deep-yellow, basic mercuric sulfate. The mixture

is stirred and heated to 55° under nitrogen, and 82.0 g. (101 ml., 1.0 mole) of cyclohexene (Note 1) is added at once. A temperature of 55–65° (Note 2) is maintained for 1 hour. During this time the color of the reaction mixture changes from a deep yellow to the cream color of the cyclohexene-mercuric sulfate complex.

At the end of 1 hour the condenser is set for distillation. The temperature of the reaction mixture is raised (Note 3), the mixture is stirred while a slow current of nitrogen is continued, and 300 ml. of mixture of crude cyclopentanecarboxaldehyde and water is distilled over a period of approximately 2 hours. The crude product is removed in a separatory funnel from the aqueous layer, which is extracted with three 50-ml. portions of ether. The extracts are combined with the product and dried over anhydrous sodium sulfate. The solution is filtered into a 250-ml. Claisen flask set for vacuum distillation, the pressure is gradually reduced to 100 mm. to distil ether, and the cyclopentanecarboxaldehyde is distilled rapidly (Note 4) at 74–78° (100 mm.). The yield of aldehyde (n_D^{20} 1.4420–1.4428) is 45–52 g. (46–53%).

Unless the aldehyde is to be used immediately, it is stored in a brown bottle at 0° after the addition of 0.1 g. of hydroquinone and a blanket of nitrogen (Note 5).

2. Notes

1. Cyclohexene from an unopened bottle or freshly distilled material (b.p. 82–84°) is used.

2. This is the optimal temperature range to form the cyclohexene-mercuric sulfate complex.^{2, 3}

3. The complex undergoes oxidation-reduction at about 100° to give cyclopentanecarboxaldehyde, mercurous sulfate, and some mercury. If desired, the mercury products can be regenerated to mercuric sulfate:

The water and sludge of mercurous sulfate and mercury, which remain after the distillation of cyclopentanecarboxaldehyde, are filtered with suction, washed with three 100-ml. portions of boiling water, three 100-ml. portions of acetone, and finally with three 100-ml. portions of boiling water. The gray-black solid is sucked dry.

To the solid in a 3-l. Erlenmeyer flask is added 270 ml. of water, then 90 g. (65 ml., 1.0 mole) of concentrated nitric acid *slowly* (*Hood!*). The contents of the flask are swirled and allowed to stand until frothing and evolution of reddish brown oxides of nitrogen subsides. Dow-Corning Antifoam A helps to control frothing.

The mixture is heated *cautiously* on a hot plate to avoid excess frothing. When the frothing has almost subsided, additional concentrated nitric acid is added, 90 g. (65 ml., 1.0 mole) at a time, with swirling and intermittent heating to control the vigorous reaction. The solid changes from gray-black to a cream color after six 90-g. portions of concentrated nitric acid have been used.

Six hundred milliliters of concentrated nitric acid is then added with heating to form a clear, deep-orange solution of mercuric nitrate. This mixture is allowed to cool and is then filtered with suction through sintered glass to remove a small amount of solid.

Four hundred and sixty grams (250 ml., 4.7 moles) of concentrated sulfuric acid is added to the filtrate to precipitate mercuric sulfate. The mixture is boiled under the hood for 1 hour, cooled to 10–25°, and filtered with suction through sintered glass.

The solid mercuric sulfate is washed with three 100-ml. portions of approximately 40% aqueous sulfuric acid solution (110 ml. of concentrated sulfuric acid mixed with 300 ml. of water). The solid is sucked dry, transferred to an evaporating dish, broken up, and dried in the hood under a heat lamp.

The yield of recovered mercuric sulfate is 600–700 g. This material plus fresh mercuric sulfate to give 740 g. can be used in a subsequent preparation of cyclopentanecarboxaldehyde without affecting the yield.

4. Cyclopentanecarboxyaldehyde may trimerize if heating is prolonged; hence a fast, simple distillation is done. When the distillation residue is cooled, a solid may appear. This solid can be distilled above 78° (100 mm.) as a clear liquid which solidifies when allowed to stand. Recrystallization of this material from 95% ethanol gives a white solid melting at 122–124°. This product was shown to be cyclopentanecarboxaldehyde trimer by

a mixed melting-point determination with trimer prepared from cyclopentanecarboxyaldehyde and 85% phosphoric acid.⁴

5. During storage there is a slow formation of cyclopentanecarboxaldehyde trimer.

3. Methods of Preparation

Cyclopentanecarboxaldehyde has been prepared by the procedure described above;^{2,3} by the reaction of aqueous nitric acid and mercuric nitrate with cyclohexene;⁵ by the action of magnesium bromide etherate⁶ or thoria⁷ on cyclohexene oxide; by the dehydration of *trans*-1,2-cyclohexanediol over alumina mixed with glass helices;⁸ by the dehydration of divinyl glycol over alumina followed by reduction;⁹ by the reaction of cyclopentene with a solution of $[\text{HFe}(\text{CO})_4]^-$ under a carbon monoxide atmosphere;¹⁰ and by the reaction of cyclopentadiene with dicobalt octacarbonyl under a hydrogen and carbon monoxide atmosphere.¹¹

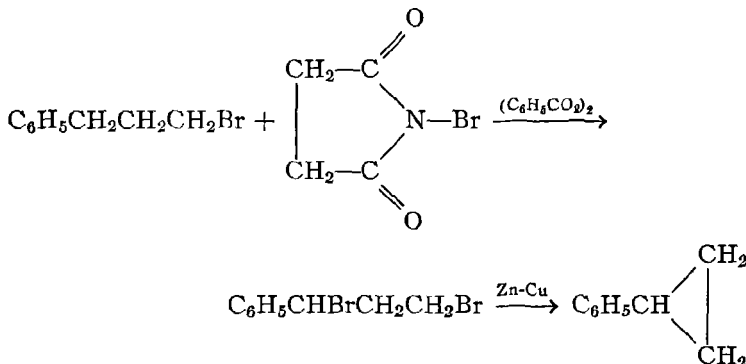
4. Merits of the Preparation

This procedure uses readily available starting materials and in one operational step generally gives higher yields of cyclopentanecarboxaldehyde than other preparations described in the literature. Because mercuric sulfate is an expensive reactant, a method of regenerating the mercury products is given. Cyclopentanecarboxaldehyde is a useful intermediate for many cyclopentane derivatives.

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CYCLOPROPYLBENZENE

(Benzene, cyclopropyl-)

Submitted by THOMAS F. CORBIN, ROGER C. HAHN,¹
and HAROLD SHECHTER²

Checked by WILLIAM G. DAUBEN and PAUL LAUG

1. Procedure

Caution! N-Bromosuccinimide is a skin irritant.

A. *1,3-Dibromo-1-phenylpropane*. In a 3-l. three-necked flask fitted with a sealed stirrer and two efficient reflux condensers are placed 199 g. (1.0 mole) of 1-bromo-3-phenylpropane (Note 1), 187 g. (1.05 moles) of N-bromosuccinimide (Note 2), 3 g. of benzoyl peroxide, and 1.2 l. of carbon tetrachloride. The mixture is heated cautiously with a flame to reflux until a spontaneous reaction starts; ice-bath cooling is then applied if necessary (Note 3). When the spontaneous reaction subsides, the stirring is stopped; if more than a negligible amount of N-bromosuccinimide remains in the bottom of the flask (succinimide rises to the surface of the solvent), heating and stirring are continued until an evolution of hydrogen bromide is noted. The mixture is cooled, and the solids are removed by suction filtration and washed with carbon tetrachloride. The washings are combined with the original filtrate, and the bulk of the carbon tetrachloride

is removed (Note 4) by distillation at water aspirator pressure and a bath temperature of 40–50° (Note 5). The remainder of the solvent is removed at the same bath temperature and at 0.1 mm. pressure (Note 6). The orange-yellow residue (nearly 100% of the theoretical yield of 1,3-dibromo-1-phenylpropane) is used without further purification (Note 7) in the next step.

B. *Cyclopropylbenzene*. In a 1-l. three-necked flask equipped with a stirrer and a thermometer extending into the flask but free from the stirrer are placed 500 ml. of redistilled dimethylformamide and zinc-copper couple prepared from 131 g. (2 g. atoms) of zinc (Note 8). The mixture is cooled to 7° in an ice bath, and 1,3-dibromo-1-phenylpropane is added to the stirred mixture at a rate sufficient to maintain the reaction temperature at 7–9° (Note 9). The mixture is stirred for 30 minutes after the addition is completed, poured into 1 l. of water, and then steam-distilled until the condensate is homogeneous or 1 l. of water has been collected. The organic layer is separated from the distillate, and the aqueous layer is extracted with three 100-ml. portions of ether. The combined organic portions are washed with four 50-ml. portions of water and dried over anhydrous potassium carbonate. The ether is removed by distillation at atmospheric pressure at water bath temperature. The residue is distilled to give 88–100 g. (75–85%) of cyclopropylbenzene, b.p. 170–175° (Note 10), n_D^{26} 1.5306–1.5318.

2. Notes

1. The 1-bromo-3-phenylpropane was obtained from Columbia Organic Chemicals Co., Inc., Columbia, South Carolina, and from Aldrich Chemical Co., Inc., Milwaukee, Wisconsin. Redistillation of the commercial material does not noticeably affect yields.

2. N-Bromosuccinimide was obtained from Arapahoe Chemicals, Inc., Boulder, Colorado, and from Coleman and Bell, Norwood, Ohio. The material utilized by the checkers was shown to be 98.6% pure by iodometric analyses.

3. This reaction may become vigorously exothermic; two condensers and a highly mobile setup, allowing quick (5 seconds) removal of heat and application of cooling, are then necessary to

contain it. *Caution* must be taken to control but not stop the reaction.

4. Any bromine present at this point is entrained by the carbon tetrachloride; the separated carbon tetrachloride may be purified by shaking with a small quantity of sodium bisulfite, drying over anhydrous potassium carbonate, and distilling.

5. Higher bath temperatures cause darkening of the residue with evolution of hydrogen bromide.

6. An efficient dry ice trap is essential to protect the vacuum pump.

7. Attempts to distil the residue usually cause evolution of large amounts of hydrogen bromide.

8. Zinc powder, obtainable from Mallinckrodt Chemical Works, St. Louis, Missouri, and Merck and Co., Rahway, New Jersey, is placed in a beaker and is washed consecutively and *rapidly* (~ 10 seconds) with three 100-ml. portions of 3% hydrochloric acid, two 100-ml. portions of water, two 200-ml. portions of 2% aqueous copper sulfate (until blue color disappears), two 200-ml. portions of water, two 100-ml. portions of acetone, two 100-ml. portions of dimethylformamide, and is washed into the reaction vessel with dimethylformamide. This procedure is a modification of one described by Hennion and Sheehan.³

9. This *highly exothermic* reaction often has an induction period the end of which is characterized by a rapid temperature rise dependent on the amount of dibromide already added. At the first sign of reaction (*watch the thermometer closely*), addition of dibromide should be stopped and should be resumed only after the temperature has stopped rising. Careful purification of the dimethylformamide appears to minimize the induction period.

10. Analysis of this product by gas liquid chromatography (QF-1 coated column, 130°) showed it to be $>98.5\%$ pure. The boiling point of a sample collected by chromatography was $169\text{--}171^{\circ}$.

3. Methods of Preparation

Cyclopropylbenzene has been prepared by decomposition of 5-phenylpyrazoline,⁴ addition of hydrogen bromide to cinnamyl bromide followed by cyclization with zinc,⁵ decarboxylation of

1-phenylcyclopropanecarboxylic acid,⁶ reaction of magnesium with 3-bromo-3-phenyl methyl ether followed by decomposition of the intermediate Grignard reagent,⁷ reaction of styrene with methylene iodide and zinc-copper couple,⁸ reaction of sodium amide with 3-phenylpropyltrimethylammonium iodide in liquid ammonia,⁹ decarbonylation of 1-phenylcyclopropanecarboxaldehyde,¹⁰ and reaction of sodium hydroxide with (1-phenylcyclopropyl)-diphenylphosphine oxide.¹¹

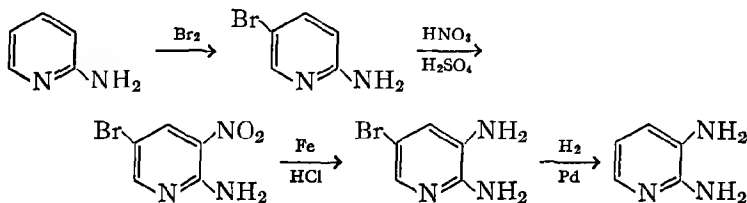
4. Merits of the Preparation

Because of the unique properties of the cyclopropane ring, cyclopropylbenzene is a compound of considerable interest. Only one of the alternative methods⁹ for the preparation of this compound has been reported to give more than 32% yield; the procedure described affords an olefin-free product without a relatively laborious purification process. By its utilization of readily available starting materials, and by its applicability to the preparation of large quantities of product, this method of synthesis provides easy access to many cyclopropylbenzene derivatives.¹²

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2,3-DIAMINOPYRIDINE

(Pyridine, 2,3-diamino-)

Submitted by B. A. FOX¹ and T. L. THERLFAH²

Checked by MAX TISHLER, G. A. STEIN, G. LINDBERG, and M. RYDER

1. Procedure

Caution! The bromination and nitration steps should be carried out in a well-ventilated hood.

A. 2-Amino-5-bromopyridine. In a 2-l. three-necked flask equipped with stirrer, dropping funnel, and condenser is placed a solution of 282 g. (3.0 moles) of 2-aminopyridine (Note 1) in 500 ml. of acetic acid. The solution is cooled to below 20° by immersion in an ice bath, and 480 g. (154 ml., 3.0 moles) of bromine dissolved in 300 ml. of acetic acid is added dropwise with vigorous stirring over a period of 1 hour. Initially the temperature is maintained below 20°, but after about half the bromine solution has been added it is allowed to rise to 50° to delay as long as possible the separation of the hydrobromide of 2-amino-5-bromopyridine. At 50° the hydrobromide usually begins to crystallize when about three-quarters of the bromine has been added. When addition of bromine is completed, the mixture is stirred for 1 hour and is then diluted with 750 ml. of water to dissolve the hydrobromide. The contents of the flask are transferred to a 5-l. beaker and are neutralized, with stirring and cooling, by the addition of 1.2 l. of 40% sodium hydroxide solution.

The precipitated 2-amino-5-bromopyridine, contaminated with some 2-amino-3,5-dibromopyridine, is collected by filtration and,

after washing with water until the washings are free of ionic bromide, is dried at 110° (Note 2). The 2-amino-3,5-dibromopyridine is removed from the product by washing with three 500-ml. portions (Note 3) of hot petroleum ether (b.p. 60–80°). The yield of 2-amino-5-bromopyridine, m.p. 132–135°, sufficiently pure for use in the next stage, is 320–347 g. (62–67%) (Notes 4 and 5).

B. *2-Amino-5-bromo-3-nitropyridine*. A 1-l. three-necked flask immersed in an ice bath and equipped with stirrer, dropping funnel, condenser, and thermometer is charged with 500 ml. of sulfuric acid (sp. gr. 1.84), and 86.5 g. (0.5 mole) of 2-amino-5-bromopyridine is added at such a rate that the temperature does not exceed 5°. Twenty-six milliliters (39 g., 0.57 mole) of 95% nitric acid is added dropwise with stirring at 0°, and the mixture is stirred at 0° for 1 hour, at room temperature for 1 hour, and at 50–60° for 1 hour. The contents of the flask are cooled and poured onto 5 l. of ice and neutralized with 1350 ml. of 40% sodium hydroxide solution. The yellow precipitate of 2-amino-5-bromo-3-nitropyridine is collected by filtration and washed with water until the washings are free of sulfate, slightly acidulated water being used at the end to prevent colloidal breakthrough. The product is dried at room temperature to constant weight. The yield of 2-amino-5-bromo-3-nitropyridine, m.p. 204–208°, sufficiently pure for the next stage, is 85–93 g. (78–85%) (Notes 6 and 7).

C. *2,3-Diamino-5-bromopyridine* (Note 8). A 100-ml. flask fitted with a reflux condenser is charged with 10.9 g. (0.05 mole) of 2-amino-5-bromo-3-nitropyridine, 30 g. of reduced iron, 40 ml. of 95% ethanol, 10 ml. of water, and 0.5 ml. of concentrated hydrochloric acid (Notes 9 and 10). The mixture is heated on a steam bath (Note 11) for 1 hour, and at the end of this period the iron is removed by filtration and is washed three times with 10-ml. portions of hot 95% ethanol. The filtrate and washings are evaporated to dryness, and the dark residue is recrystallized from 50 ml. of water, 1 g. of activated carbon being used and the mixture being filtered while hot. The charcoal is washed with hot ethanol to avoid losses. 2,3-Diamino-5-bromopyridine crystallizes as colorless needles, m.p. 163°. The yield is 6.5–7.1 g. (69–76%).

D. *2,3-Diaminopyridine* (Note 12). In an apparatus for catalytic hydrogenation (Note 13) 56.4 g. (0.3 mole) of 2,3-diamino-5-bromopyridine suspended in 300 ml. of 4% sodium hydroxide solution is shaken with hydrogen in the presence of 1.0 g. of 5% palladized strontium carbonate (Note 14). When absorption of hydrogen is completed, the catalyst is removed by filtration, and, after saturation with potassium carbonate (about 330 g. is required), the resulting slushy mixture is extracted continuously with ether until all the precipitate completely disappears (usually about 18 hours, but this depends on the efficiency of the extraction apparatus). The ether is removed by distillation, and the residue of crude 2,3-diaminopyridine is recrystallized from benzene (about 600 ml. is required) using 3 g. of activated charcoal and filtering rapidly through a preheated Büchner funnel. The yield of 2,3-diaminopyridine, obtained as colorless needles, m.p. 115–116°, pK_a 6.84, is 25.5–28.0 g. (78–86%) (Note 15).

2. Notes

1. The checkers used a pure grade of 2-aminopyridine (m.p. 58–60°) obtained from Matheson, Coleman and Bell.

2. The checkers dried their product at room temperature to constant weight in order to avoid loss of product due to its high volatility at 110°. It was found that 95% of an aliquot had sublimed during drying for 24 hours at 110° and atmospheric pressure. The residue analyzed high in bromine, indicating that the monobromo derivative is more volatile than the dibromo derivative.

3. The checkers washed their crude product by first refluxing its suspension in 600 ml. of petroleum ether (b.p. 60–71°) for about 20 minutes. The product, obtained by filtration, was slurry-washed on the funnel with two 600-ml. portions of boiling petroleum ether followed by air-drying to constant weight.

4. The checkers' yield, for reasons outlined in Note 2, were appreciably higher. In two runs using one-half the quantities of reactants they obtained 211 g. and 224 g. (81–86%), of product, m.p. 132–133.5° and 133.5–135°, respectively; water content (K.F.) in both products was 0.2%.

5. If required, the 2-amino-5-bromopyridine may be recrystallized from benzene as colorless prisms, m.p. 137°.

6. The checkers' yield was 85.3 g. (78.2%), m.p. 202–204°.

7. Pure 2-amino-5-bromo-3-nitropyridine, yellow needles, m.p. 210°, may be obtained by recrystallizing the product from ethyl methyl ketone.

8. The method is essentially that of Petrow and Saper.³

9. Attempts to reduce larger quantities of the amino-nitro compound by this method usually give lower yields. For larger quantities several reductions may be carried out simultaneously, and the filtrates may be combined for isolation of the diamine.

10. The checkers reduced a double batch and obtained 12.8 g. (68%), m.p. 159.5–160°. In this run, heating time was doubled and charcoal was extracted repeatedly (by recycling mother liquors) to assure complete extraction.

11. The checkers employed a mechanical stirrer.

12. This is essentially the procedure of Leese and Rydon.⁴

13. The apparatus described in *Org. Syntheses*, Coll. Vol. 1, 61 (1941), or a commercial equivalent of it, is suitable.

14. The palladized strontium carbonate is prepared as follows. Suspend 33 g. of strontium carbonate in 350 ml. of water at 70°. Add 2 g. of palladium chloride dissolved in 10 ml. of concentrated hydrochloric acid, and stir the mixture at 70° for 15 minutes. Filter the mixture, wash the product thoroughly with hot water, and dry the product at 110°.

15. The checkers' yields were 74.8%–84.7% of analytically pure material giving a negative Beilstein test.

3. Methods of Preparation

2,3-Diaminopyridine has been prepared by reduction of 2-amino-3-nitropyridine with iron and aqueous acidified ethanol,³ tin and hydrochloric acid,⁵ or stannous chloride and hydrochloric acid,⁶ by catalytic reduction of 3-amino-2-nitropyridine,⁶ by reduction of 3-amino-2-nitropyridine,⁷ 2-amino-5-chloro-3-nitropyridine,⁸ or 2-amino-5-bromo-3-nitropyridine⁴ with sodium hydroxide solution and an aluminum nickel alloy, and by catalytic reduction of 2-amino-5-bromo-3-nitropyridine.⁴ Amination of

3-aminopyridine with sodamide ⁹ and of 3-amino-2-chloropyridine with concentrated aqueous ammonia ¹⁰ have also been employed.

4. Merits of the Preparation

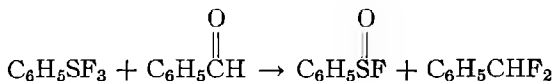
By this method of preparation 2,3-diaminopyridine is obtained in 26–43% yield from the readily available 2-aminopyridine. The intermediates 2-amino-5-bromopyridine and 2-amino-5-bromo-3-nitropyridine are prepared in higher yields than previously recorded.

Methods of preparation of 2,3-diaminopyridine which involve the reduction of 2-amino-3-nitropyridine are laborious. The material is obtained in yields of less than 10% by nitration of 2-aminopyridine, and its separation from 2-amino-5-nitropyridine, which is the major product of the nitration, is tedious and inconvenient. Reduction of amino-nitro or amino-halo-nitro compounds with sodium hydroxide solution and an aluminum nickel alloy gives variable yields of an inferior product, and the method can be used only for preparing comparatively small quantities of 2,3-diaminopyridine. Catalytic reduction of 3-amino-2-nitropyridine gives a good yield of 2,3-diaminopyridine, but preparation of the amino-nitro compound is a difficult and time-consuming process. The method of Schickh, Binz, and Schulz,¹⁰ which involves chlorination of 3-aminopyridine to 3-amino-2-chloropyridine and amination of the latter by heating for 20 hours at 130° with concentrated aqueous ammonia, suffers from the disadvantage that 3-aminopyridine is less readily available than is 2-aminopyridine. Furthermore the yields obtained in the amination stage are somewhat erratic, and the yields obtained by the submitters never approached the 57% reported.

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2. Department of Chemistry, Color Chemistry and Dyeing, Huddersfield College of Technology, Huddersfield, England.
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α,α -DIFLUOROTOLUENE
(Toluene, α,α -difluoro-)
AND BENZENESULFINYL FLUORIDE



Submitted by WILLIAM A. SHEPPARD¹

Checked by E. S. GLAZER and JOHN D. ROBERTS

1. Procedure

Caution! Phenylsulfur trifluoride is toxic, and this reaction should be carried out in a good hood. The reagent should not be allowed to come in contact with the skin.

Phenylsulfur trifluoride² (16.6 g., 0.10 mole) is placed in a two-necked 50-ml. flask equipped with a dropping funnel and connected to a dry distillation column (Note 1). The flask is heated to 50–70° in an oil bath, and 10.6 g. (0.10 mole) of benzaldehyde is added in small portions over 30 minutes. A mild exothermic reaction occurs. After the addition is completed, the reaction flask is heated to 100° with an oil bath, and the pressure on the column is reduced until α,α -difluorotoluene distills. The major portion of product distills at 68° (80 mm.), but a small final cut, b.p. 45° (15 mm.), is obtained. The yield of α,α -difluorotoluene is 9.2–10.2 g. (71–80%) (Note 2). The pressure is reduced and the distillation is continued. An intermediate cut of 1–2 g., b.p. 45° (15 mm.) to 60° (2.5 mm.), is discarded, and benzenesulfinyl fluoride, 11.7–13.2 g. (81–91%), b.p. 60° (2.5 mm.), is collected. Since the benzenesulfinyl fluoride slowly attacks glass and may be unstable to storage at room temperature, it is recommended that this product be stored at –80°.

2. Notes

1. A 45-cm. spinning band column was employed by the submitter, but any distillation column with a low holdup may be used. Since the products have widely different boiling points, careful fractionation during distillation is not needed. Because the phenylsulfur trifluoride and benzenesulfinyl fluoride slowly attack glass, all equipment should be rinsed with water and acetone *immediately* after use to minimize etching.

2. The product attacks glass slowly on standing, and a moderate increase in pressure takes place. The product can be stored for a period of several days in a polyethylene bottle, but it is best to prepare the material shortly before use. If prolonged storage is required, a stainless steel cylinder or a bottle fabricated from Teflon[®] polytetrafluoroethylene resin is suggested.

3. Methods of Preparation

α,α -Difluorotoluene has been prepared by the reaction of α,α -dichlorotoluene with antimony(III) fluoride,³ by the hydrogenation of α -chloro- α,α -difluorotoluene,⁴ by the action of sulfur tetrafluoride on benzaldehyde,⁵ and by the present method.^{6,7}

4. Merits of the Preparation

Sulfur tetrafluoride provides an inexpensive method for selectively converting a carbonyl to a difluoromethyl group. However, the reactions involving sulfur tetrafluoride, in general, require pressure equipment constructed of fluorine-resistant material such as "Hastelloy-C" bombs.⁸ Phenylsulfur trifluoride may be used to advantage for the same reaction, where small amounts are involved, since the reaction may be run at atmospheric pressure in glass, polyethylene, or metal containers.

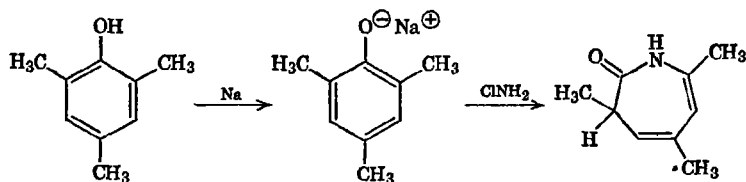
Although the sulfur trifluoride compounds are generally useful as selective agents for conversion of carbonyl and carboxyl groups to difluoromethylene and trifluoromethyl groups, variations in reaction conditions are often necessary.⁷ Thus the reaction of aromatic ketones requires heating at 150°. Since the reaction with aliphatic aldehydes and ketones is exothermic, it is advan-

tageous to run it in a solvent such as methylene chloride or acetonitrile containing a small amount of sodium fluoride powder (with ketones an induction period of several hours may be observed). Reactions with carboxylic acids should be carried out in a container resistant to hydrogen fluoride, and they require heating at 120° to 150°.

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1,3-DIHYDRO-3,5,7-TRIMETHYL-2H-AZEPIN-2-ONE

(2H-Azepin-2-one, 1,3-dihydro-3,5,7-trimethyl-)



Submitted by LEO A. PAQUETTE¹

Checked by KLAUS HERBIG and B. C. MCKUSICK

1. Procedure

Caution! Because obnoxious fumes are liberated during the reaction with chloramine, the apparatus should be set up in a well-ventilated hood.

Five hundred forty-five grams (4.00 moles) of 2,4,6-trimethylphenol (Note 1) is placed in a 1-l. three-necked flask fitted with mechanical stirrer, thermometer, 90-cm. Vigreux column, and dropping funnel (not of the pressure-equalizing variety). The

Vigreux column must extend sufficiently into the top of a well-ventilated hood to entrain effectively the fumes that will be generated later in the operation. The phenol is melted with the aid of an external oil bath or Glascol[®] heating mantle and heated to about 100°. The heating bath is removed, and 27.6 g. (1.20 g. atoms) of sodium in cubes about 1 cm. on a side or smaller is added to the stirred mixture at such a rate that the temperature does not exceed 150–160°. The molten mass gradually becomes dark red in color as the sodium dissolves. While the addition and solution of the sodium is proceeding, a cold solution of about 0.25 mole of chloramine in 250 ml. of ether is prepared (Note 2).

When all the sodium has dissolved, the phenoxide-phenol mixture is heated to 150°. With the oil bath or heating mantle still surrounding the flask, *and with a protective shield between the reaction vessel and the operator* (Note 3), the cold ethereal chloramine solution is added with rapid stirring in a thin stream from the dropping funnel at such a rate that the temperature of the reaction mixture does not drop below 125°. Best results are obtained if the thin stream of ether solution can be added directly to the molten mass without first touching the walls of the flask.

When the addition is completed, the heat source is removed and the dark-colored contents are allowed to cool until another 0.25 mole of ethereal chloramine has been prepared and is ready for use; a wait of 1.5–2 hours between chloramine additions is convenient but not essential to the success of the experiment. The cooled reaction mixture is then reheated to 150°, and the process is repeated. This sequence is repeated until a total of four 0.25-mole portions of chloramine are added.

The reaction mixture is allowed to cool. The dropping funnel, thermometer, and Vigreux column are replaced with a stopper and short-path distillation head. The mixture is stirred while the excess phenol is removed by distillation at water-aspirator pressure; b.p. 105–110° (14 mm.). When the temperature begins to rise above 110° (14 mm.), the distillation is stopped and the residue is allowed to cool (Note 4).

Water (500 ml.) and 500 ml. of ether are added to the residue, and the mixture is well stirred. The mixture is transferred to a

2-l. separatory funnel, and the two layers are carefully separated. The aqueous layer is extracted with two additional 250-ml. portions of ether. The combined organic layers are washed twice with 5% sodium hydroxide solution and then with water, dried over anhydrous magnesium sulfate, filtered, and evaporated on a rotary evaporator. The dark residue is transferred to a distillation flask and distilled through a 30-cm. Vigreux column to yield a crystalline fraction, b.p. 130–155° (13 mm.) (Note 5). Recrystallization of this distillate from ligroin gives 68–80 g. (45–53%, based on chloramine added) of 1,3-dihydro-3,5,7-trimethyl-2H-azepin-2-one as a fluffy white solid, m.p. 131–132°.

2. Notes

1. Suitable material is obtainable from the Aldrich Chemical Co., Milwaukee, Wisconsin.

2. The ethereal chloramine solution is conveniently prepared in this quantity according to the precise directions of Coleman and Johnson.² It is essential to the success of this reaction that their procedure be followed exactly.

3. The protective shield is recommended despite the fact that no fire or explosion has been observed in well over fifty such experiments by the submitter.

4. The phenol recovered at this stage is reusable in subsequent preparations.

5. It is not always necessary to distil the residue. The checkers obtained a tan crystalline residue that was recrystallized from about 2 l. of heptane to give 68 g. of colorless azepinone, m.p. 130–132°. An additional 12 g. of the azepinone with the same appearance and melting point was obtained by concentrating and cooling the heptane filtrate.

3. Methods of Preparation

1,3-Dihydro-2H-azepin-2-one has been prepared in a lengthy five-step sequence by Vogel and Erb.³ The present method,⁴ the reaction of sodium 2,6-dialkylphenoxides with chloramine, easily affords the corresponding dihydroazepinones in good yield.

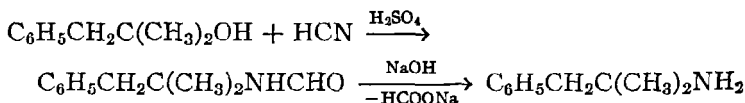
4. Merits of the Preparation

This reaction can be generally applied with equal success to other 2,6-dialkylphenols,⁴ many of which are commercially available. Although the procedure cannot be extended to phenol or *o*-monosubstituted phenols (aminophenols result ⁵), it represents a facile synthetic method for obtaining a ring system heretofore relatively unavailable. The dihydroazepinones in turn are excellent starting materials for the preparation of other novel heterocyclic systems such as 2,3-dihydro-1H-azepines,⁶ 2-substituted-3H-azepines,⁷ and derivatives of 2-azabicyclo[3.2.0]hept-6-ene.⁸

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α,α -DIMETHYL- β -PHENETHYLAMINE

(Phenethylamine, α,α -dimethyl)



Submitted by JOHN J. RITTER¹ and JOSEPH KALISH²

Checked by WILLIAM G. DAUBEN and ALAN KRUBINER

1. Procedure

Caution! This preparation should be conducted in a hood because poisonous hydrogen cyanide may be evolved.

A. *N*-Formyl- α,α -dimethyl- β -phenethylamine. To a 2-l., three-necked, round-bottomed flask fitted with a sealed stirrer carrying

a crescent-shaped blade, a thermometer, an addition funnel, and a reflux condenser connected to a trap containing 20% sodium hydroxide solution is added 500 ml. of glacial acetic acid (Note 1). The contents of the flask are cooled to 20° by means of an ice bath, the addition funnel is temporarily replaced by a stopper, and to the stirred acetic acid is added 110 g. (2 moles) of 95% sodium cyanide in small portions. The temperature of the mixture is maintained around 20°, and the addition requires about 20 minutes (Note 2). The addition funnel is replaced, and a previously prepared and cooled solution of 500 g. (272 ml., 4.9 moles) of concentrated sulfuric acid in 250 ml. of glacial acetic acid is added slowly, with stirring, the temperature of the mixture being kept at about 20° by means of an ice bath (Note 3). The ice bath is removed, and 300 g. (2 moles) of α,α -dimethyl- β -phenethyl alcohol (Note 4) is added over a 20-minute period during which the temperature of the mixture rises slowly to 35–45°. The reaction mixture is stirred for an additional 90 minutes (Note 5) and allowed to stand overnight. The amber-colored mixture containing some solid sodium sulfate is aerated with nitrogen for 2 hours (*Caution! In a hood*), poured into 3 l. of ice water, and the supernatant oil separated. The aqueous phase is neutralized with sodium carbonate and extracted with 600 ml. of ether. The ethereal extract is combined with the original oily supernatant, neutralized with sodium carbonate, and dried over anhydrous sodium sulfate. The solvent is removed under reduced pressure, and the residue is distilled to yield 230–248 g. (65–70%) of product, b.p. 137–141° (2 mm.). Redistillation of the ether-containing fore-run yields up to an additional 14 g. of material.

B. *α,α -Dimethyl- β -phenethylamine*. In a 3-l., three-necked, round-bottomed flask equipped with a reflux condenser and a sealed stirrer are placed 246 g. (1.39 moles) of N-formyl- α,α -dimethyl- β -phenethylamine and 2.1 l. of 20% sodium hydroxide solution. The mixture is heated under reflux with vigorous stirring for 2.5 hours or until a test portion of the oily layer dissolves completely in cold 5% hydrochloric acid. The reaction mixture is cooled, 750 ml. of benzene is added, the mixture is stirred, and the benzene layer is separated. The benzene solution is shaken with a saturated sodium chloride solution, the benzene removed

by distillation at atmospheric pressure, and the product distilled at reduced pressure to yield 155–165 g. (75–80%) of α,α -dimethyl- β -phenethylamine, b.p. 80–82° (10 mm.).

2. Notes

1. The reaction may be conducted in other solvents (e.g., dibutyl ether) or in the absence of solvent with some alteration in the order of mixing the reagents. The submitters find for this and a large number of similar preparations that acetic acid generally is most convenient.

2. Most of the sodium cyanide does not dissolve.

3. Care must be taken during the first part of the addition because the reaction is very exothermic.

4. Methallylbenzene or isobutenylbenzene may be used in place of the carbinol with practically identical results.

5. The temperature may continue to rise during the initial portion of this period, but it is controlled by means of an ice bath to limit the temperature of the mixture to 45–50°.

3. Methods of Preparation

α,α -Dimethyl- β -phenethylamine has been prepared from benzaldehyde and 2-nitropropane³ and from isobutyrophenone by a series of steps involving alkylation with benzyl bromide, alkali cleavage, and Hofmann bromamide degradation.⁴

4. Merits of the Preparation

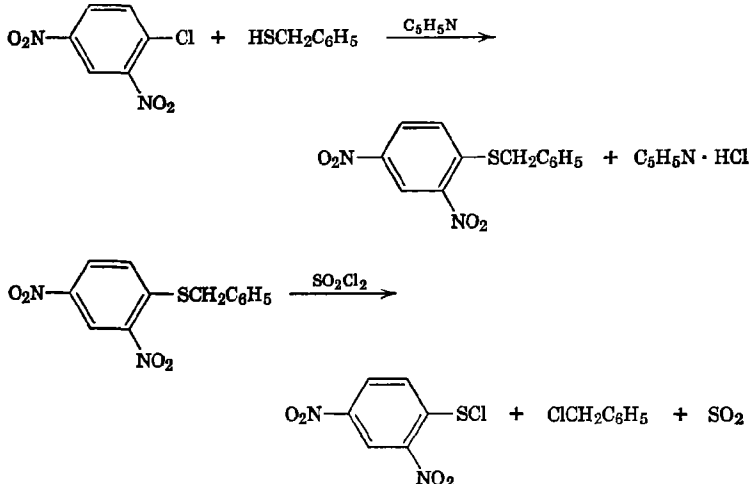
The present method is shorter and less laborious than previously described methods, and it gives better yields of material. The method is one of considerable scope,⁵⁻⁸ having been used with fair to excellent success with many tertiary alcohols or the corresponding alkenes, with benzyl alcohol, and with some secondary alcohols. Nitriles (except cyanogen and phenylacetoneitrile) generally have been found to react at satisfactory rates and in good yield.

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2,4-DINITROBENZENESULFENYL CHLORIDE

(Benzenesulfonyl chloride, 2,4-dinitro-)



Submitted by NORMAN KHARASCH and ROBERT B. LANGFORD¹

Checked by D. C. DITTMER and B. C. MCKUSICK

1. Procedure

Caution! Both steps should be carried out in a good hood.

A. *2,4-Dinitrophenyl benzyl sulfide.* The apparatus consists of a 1-l., three-necked, round-bottomed flask equipped with a sealed

mechanical stirrer and a reflux condenser. In it are placed 202 g. (1.00 mole) of 2,4-dinitrochlorobenzene (m.p. 50–52°) (*Caution! A skin irritant*), 400 ml. of methanol, 124 g. (1.00 mole) of benzyl mercaptan, and 87 g. (85 ml., 1.10 moles) of pyridine. The mixture is heated at the reflux temperature with stirring for 16 hours or more (Note 1) and cooled to 0°. The 2,4-dinitrophenyl benzyl sulfide that precipitates is separated by filtration, washed with two 250-ml. portions of ice-cold methanol, and dried at 60–80°. The sulfide, a yellow crystalline solid that melts at 128–129°, weighs 235–250 g. (81–86%) (Note 2). It may be used in the next step without further purification.

B. *2,4-Dinitrobenzenesulfenyl chloride*. Dry 2,4-dinitrophenyl benzyl sulfide (232 g., 0.80 mole) and 400 ml. of dry ethylene chloride are placed in a 2-l., one-necked, round-bottomed flask equipped with a stirrer (Note 3). Sulfuryl chloride (119 g., 0.88 mole) (Note 4) is added to the resulting suspension at room temperature. A mildly exothermic reaction causes the solid to dissolve quickly, usually within 1 to 2 minutes, with a temperature rise of 10–15° (Note 5). The resulting clear yellow solution is concentrated to an oil by heating under aspirator vacuum on a steam bath (Note 6). (*Caution! Do not heat with gas or electricity because the product, like many nitro compounds, can explode if overheated.*) The residual oil is cooled to 50–60°, and 3–4 volumes of dry petroleum ether (b.p. 30–60°) are added with vigorous hand-swirling. The oil quickly crystallizes. The mixture is cooled to room temperature and filtered to separate 2,4-dinitrobenzenesulfenyl chloride as a yellow crystalline solid. The sulfenyl chloride is washed well with dry petroleum ether and dried at 60–80° (Note 7); weight 150–170 g. (80–90%); m.p. 95–96° (Notes 8, 9).

2. Notes

1. After 2 or 3 hours, solid product usually appears in the reaction mixture.

2. When practical grade 2,4-dinitrochlorobenzene (m.p. 46–47°) is substituted, a product of equally good quality (m.p. 128–129°) is obtained, but the yield is only 70–75%.

3. All materials and equipment used in Step B of this procedure must be completely dry to avoid loss of product by hydrolysis. The checkers found, however, that the reaction may be carried out open to the air without loss of yield.

4. Practical grade sulfuryl chloride, obtained from Matheson, Coleman and Bell, gives satisfactory results.

5. The 2,4-dinitrophenyl benzyl sulfide normally undergoes cleavage at room temperature without the addition of a catalyst. If the reaction does not occur spontaneously, the mixture may be warmed gently and/or one drop of dry pyridine may be added to initiate the reaction.

6. Rotary or other distillation equipment with metal parts should not be used in concentrating the reaction mixture because not only will the corrosive vapors damage the equipment, but also the resulting metal salts will discolor and partially decompose the product. The solution should not be heated any longer than is necessary to concentrate it; excessive heating gives a dark-colored product.

7. The product should not be dried longer than is necessary for it to reach constant weight, or there may be partial decomposition.

8. The product obtained by this procedure is pure enough for most purposes. Its melt, however, is faintly cloudy. A product of high purity, giving a clear melt, can be obtained by recrystallization from about 15 ml. of dry carbon tetrachloride per gram of sulfenyl chloride. When stored in a sealed brown bottle with a plastic cap (no metal!), the sulfenyl chloride is stable for years.

9. 2,4-Dinitrobenzenesulfenyl bromide may be similarly prepared by refluxing 2,4-dinitrophenyl benzyl sulfide with the equivalent amount of bromine in 5 parts of dry carbon tetrachloride. As it is less stable than the chloride, losing bromine if overheated, it should be concentrated on a 40° water bath under vacuum. When worked up in the same manner as the chloride, the product usually contains some *bis*-(2,4-dinitrophenyl) disulfide. Because the disulfide is insoluble in carbon tetrachloride, the sulfenyl bromide may be readily purified by recrystallization; yield 75-80%, m.p. 102-104°.

3. Methods of Preparation

2,4-Dinitrophenyl benzyl sulfide has been prepared by the reaction of benzyl chloride with 2,4-dinitrothiophenol² or *bis*-(2,4-dinitrophenyl) disulfide³ and by the condensation of 2,4-dinitrochlorobenzene with benzyl mercaptan.⁴

2,4-Dinitrobenzenesulfonyl chloride has been obtained by the chlorinolysis of 2,4-dinitrophenyl thiolbenzoate,⁵ 2,4-dinitrothiophenol,⁶ or *bis*-(2,4-dinitrophenyl) disulfide,^{7,11} and by the present procedure.⁸

4. Merits of the Preparation

2,4-Dinitrobenzenesulfonyl chloride is a versatile analytical reagent for the characterization of a wide variety of organic compounds, including alcohols, mercaptans, ketones, olefins, amines, aromatic compounds, olefin oxides, and hydroxysteroids. Review articles summarize these applications.^{9,10}

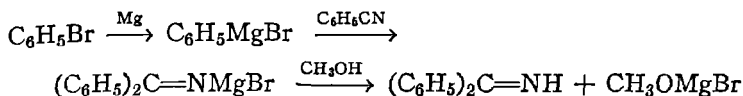
The chlorinolysis of 2,4-dinitrophenyl benzyl sulfide gives a good yield of product which is satisfactory for most purposes without recrystallization. Only simple equipment and inexpensive materials are needed, only 2 or 3 hours of the operator's time are required, and the entire procedure can be completed within 24 hours.

The best previous method of preparation, the chlorinolysis of *bis*-(2,4-dinitrophenyl) disulfide by sulfuryl chloride in the presence of pyridine,¹¹ requires much more time and effort with results that are uncertain, even for experienced operators.

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DIPHENYL KETIMINE

(Diphenylmethylenimine)

Submitted by P. L. PICKARD¹ and T. L. TOLBERT²

Checked by C. L. DICKINSON, H. D. HARTZLER, and B. C. MCKUSICK

1. Procedure

The apparatus consists of a 1-l. three-necked flask equipped with a mechanical stirrer, a 250-ml. dropping funnel, and a Friedrichs reflux condenser fitted with a calcium chloride drying tube. Magnesium turnings (13.4 g., 0.55 g. atom) and 200 ml. of anhydrous diethyl ether are put in the flask (Note 1). Slow stirring is started, and 4 ml. of bromobenzene (Note 2) is added from the funnel. After reaction has started (Note 3), the stirring rate is increased, and moderate reflux is maintained by addition of 80.5 g. of bromobenzene (making a total of 86 g. or 0.55 mole) in 100 ml. of ether. The solution is refluxed for 30–45 minutes after the addition and is cooled to room temperature. Stirring is continued while a solution of 51.5 g. (0.50 mole) of benzonitrile (Note 2) in 100 ml. of ether is added slowly enough (Note 4) to maintain only a gentle reflux. On completion of the addition, the reaction mixture of pale-yellow liquid and white solid is refluxed with stirring for 4–6 hours. The stirred mixture is cooled to room temperature, and the Grignard-nitrile complex is decomposed by cautious addition of 120 ml. (3 moles) of anhydrous methanol (Note 5).

On completion of the methanol addition, the mixture is stirred for 30 minutes and filtered. Low-boiling material is stripped from the filtrate, and the residue is distilled through a 45-cm. Vigreux column at reduced pressure. There is a fore-run, b.p. 120–127° (3.5 mm.), that weighs about 5 g. Then 55–73 g. (61–81%) of diphenyl ketimine is collected at 127–128° (3.5 mm.) or

151–152° (8 mm.); n_D^{20} 1.6180–1.6191 (Note 6). The product should be stored under nitrogen to prevent yellowing.

2. Notes

1. Freshly opened commercial (Baker and Adamson) anhydrous ether is suitable. The checkers found it more convenient to use commercial phenylmagnesium bromide than to prepare it. They obtained 80 g. (88%) of the ketimine by charging the flask with 175 ml. (0.525 mole) of 3*N* phenylmagnesium bromide (Arapahoe Chemicals, Boulder, Colorado), then adding 51.5 g. of benzonitrile as described.

2. Both bromobenzene and benzonitrile (white label grade, Eastman Kodak Company) were distilled before use.

3. If the reaction does not start spontaneously, a crystal of iodine may be added and the mixture may be warmed.

4. Care should be taken to prevent a buildup of unreacted nitrile that could result in uncontrolled reaction.

5. The methanol should be added as fast as possible. A quantity of gummy material will form as the decomposition progresses, but with continued addition of methanol it will be rapidly converted to crystalline methoxymagnesium bromide.

6. Gas chromatographic analysis of the product from three consecutive preparations showed less than 0.1% impurity. Similar results were obtained on 0.005-ml. samples in an F. and M. 202 Temperature Programed Gas Chromatograph using two columns: a 12-foot column of 10% HiVac grease and 5% Marlex-50 on 100–140 mesh Gas Chrom A, at a constant temperature of 275°, with a helium flow rate of 120 ml. per minute; and a 20-foot column of 20% GE-SE 30 on 100–140 mesh Gas Chrom A, programmed at 3.3° per minute from 250° to 300°, with a helium flow rate of 120 ml. per minute.

3. Methods of Preparation

This procedure is a modification of the method employed by Moureu and Mignonac,³ who first reported the preparation of ketimines via Grignard-nitrile complexes. The use of methanol

in the decomposition step results in higher yields and extends the method to the less stable ketimines.⁴ The preparation of diphenyl ketimine by the thermal decomposition of benzophenone oxime has been described in *Organic Syntheses*.⁵

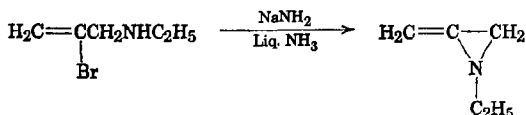
4. Merits of the Preparation

The procedure is general and is often the best way to make ketimines.

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N-ETHYLALLENIMINE

(Aziridine, 1-ethyl-2-methylene-)



Submitted by ALBERT T. BOTTINI and ROBERT E. OLSEN¹

Checked by THOMAS H. LOWRY and E. J. COREY

1. Procedure

Caution! This preparation should be carried out in a good hood to avoid exposure to ammonia. The operator should wear rubber gloves and protective goggles because 2-haloallylamines and ethyl-enimines can cause severe skin and eye irritation.

A 2-l. three-necked flask is fitted with a sealed mechanical stirrer, a gas-inlet tube, and a dry ice condenser protected from the air by a soda-lime drying tube (Note 1). The system is flushed thoroughly with dry ammonia, and 32.8 g. (0.84 mole) of sodium amide (Note 2) is added to the flask. The system is again flushed with ammonia, the condenser is provided with dry ice covered by acetone, and 1.2 l. of liquid ammonia is condensed

in the flask. The gas-inlet tube is replaced with a dropping funnel, the stirrer is started, and 118 g. (0.72 mole) of N-(2-bromoallyl)ethylamine² is added dropwise in 20–30 minutes; during the addition, the ammonia boils vigorously, and the color of the slurry changes from gray to black. Stirring is continued for 3 hours, and the dry ice is then allowed to evaporate. The condenser is provided with an ice-salt mixture, and the ammonia is allowed to evaporate until the volume is reduced to about 800 ml. (Note 3). Ethanol-free ether (200 ml.) is added rapidly through the dropping funnel, and the reaction is stopped by the slow, dropwise addition (*Caution!*) of 5 ml. of water. The ammonia is allowed to evaporate overnight. Water (150 ml.) and 100 ml. of ether are added to the residue, and the mixture is stirred for 2 minutes in order to dissolve the precipitated salts. The resulting mixture, which consists of aqueous and ethereal solutions, is separated, and the aqueous phase is extracted with 75 ml. of ether. The ether solutions are combined, dried over sodium hydroxide (Note 4), and distilled through an *efficient* low-holdup column (Note 5). The fraction with b.p. 77–80°, n_D^{25} 1.4260–1.4268, which is 96–97% N-ethylallenimine (Note 6), weighs 30–34 g. (48–55%). Pure (>99.5%) N-ethylallenimine has b.p. 77–79°, n_D^{25} 1.4281–1.4284 (Notes 7 and 8).

2. Notes

1. The glassware should be dried in an oven before use, and water must be rigorously excluded from the reaction mixture.

2. The sodium amide was obtained from Roberts Chemical Co., Nitro, West Virginia.

3. About 1.5–2.5 hours is required; stirring is continued and ice is prevented from forming on the outside of the flask. The checkers used an inner-spiral condenser cooled by ice water.

4. The ether solution and fractions taken during the subsequent distillation may be assayed by gas-liquid partition chromatography on a 0.8-cm. x 200-cm. column heated at 120° and packed with nonyl phthalate supported on ground firebrick.

5. The submitters concentrated the dry ether solution to a volume of 80–100 ml. by distillation through a 1.0-cm. x 40-cm. column packed with glass helices and equipped with a total-

reflux head. *p*-Xylene (10 ml.) was added to the residue, and this solution was fractionated through a 0.8-cm. x 30-cm. Podbielniak-type column fitted with a total-reflux head. The submitters recommend that, during distillation of the concentrated solution, a slow stream of nitrogen be passed through the boiling liquid to minimize the formation of dark, tarry products. The checkers used a 1-cm. x 100-cm. spinning-band column (Nester and Faust Co.) for the distillation of N-ethylallenimine and were able to obtain material of 99% purity (Note 7) directly.

6. This fraction is 2–3% ether, 96–97% N-ethylallenimine, and 1–2% N-ethylpropargylamine. The product from the reaction consists of 80–90% N-ethylallenimine and 10–20% N-ethylpropargylamine. N-Ethylpropargylamine has b.p. 100–102° (760 mm.), n_D^{25} 1.4314–1.4316.

7. The submitters obtained essentially pure (>99.5%) N-ethylallenimine by redistilling 30 g. or more of the 96–97% pure product through the Podbielniak column and rejecting the first 10–20% and the last 20% of the distillate. The yield of pure N-ethylallenimine is 18–21 g. (30–35%). Pure N-ethylallenimine has also been obtained in comparable yields by (a) distilling the combined concentrated solution from the equivalent of three runs through a 1.3-cm. x 100-cm. column packed with glass helices and equipped with a total-reflux head, and (b) treating the crude distillate with lithium aluminum hydride as described for the purification of N-propylallenimine.³

8. Samples of pure N-ethylallenimine and other allenimines have been stored at 0° for well over a year with no significant deterioration. *Caution! N-Alkylallenimines, even as dilute solutions in aqueous ethanol, are rapidly destroyed by acid.*^{4,5} Therefore concentrated solutions of N-alkylallenimines should not be allowed to come in contact with acid because of the possibilities of violent decomposition.

3. Methods of Preparation

The method described is essentially that of Pollard and Parcell.⁴ N-Ethylallenimine has been prepared by treating N-(2-bromoallyl)ethylamine in liquid ammonia with sodium amide,^{4,6} lithium amide,⁶ or potassium amide.⁶

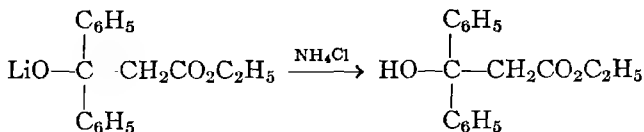
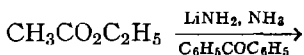
4. Merits of the Preparation

This is a general method for making N-alkylallenimines, and the following ones have been made in this way: N-methyl-,⁶ N-propyl-,⁶ N-isopropyl-,⁴ N-butyl-,⁴ N-hexyl-,⁶ and N-(3,5,5-trimethylhexyl)-.⁴ N-*t*-Butylallenimine⁶ and 1-(1-allenimino)-2-hydroxy-3-butene⁷ have also been prepared by this method, but with sodium amide/2-bromoallylamine mole ratios of 1.75 and 2.1, respectively. This method has been used for the preparation of pure N-alkylpropargylamines from 2-chloroallylamines.^{6,7} The optimum sodium amide/2-chloroallylamine ratio for the preparation of N-alkylpropargylamines is 2.1.

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ETHYL β -HYDROXY- β,β -DIPHENYLPROPIONATE

(Hydracrylic acid, 3,3-diphenyl, ethyl ester)



Submitted by W. R. DUNNAVANT and CHARLES R. HAUSER¹

Checked by WILLIAM E. PARHAM and J. E. BURCUS

1. Procedure

Caution! This preparation should be carried out in a hood to avoid exposure to ammonia.

A suspension of lithium amide (0.25 mole) (Note 1) in liquid

ammonia is prepared in a 1-l. three-necked flask equipped with a condenser, a ball-sealed mechanical stirrer, and a dropping funnel. In the preparation of this reagent commercial anhydrous liquid ammonia (500 ml.) is introduced from a cylinder through an inlet tube. To the stirred ammonia is added a small piece of clean lithium metal. After the appearance of a blue color a few crystals of ferric nitrate hydrate (about 0.25 g.) are added, followed by small pieces of freshly cut lithium metal (Note 2) until 1.73 g. has been added. After all the lithium has been converted to the amide (Note 3), 17.6 g. (0.2 mole) of ethyl acetate (Note 4) is added, and the gray suspension is stirred for about 30 seconds. To the gray suspension is added 36.4 g. (0.2 mole) of benzophenone (Note 4) dissolved in 100 ml. of anhydrous ether. The mixture is stirred for 30 minutes and is then neutralized by the addition of 13.4 g. (0.25 mole) of ammonium chloride. The liquid ammonia is then removed by use of a steam bath while 200–300 ml. of ether is being added (Note 5). When the ammonia has been removed, 200 ml. of cold water is added. The ether layer is separated, and the aqueous layer is further extracted with two 100-ml. portions of ether. The combined ether extract is dried over magnesium sulfate and filtered, and the solvent is evaporated. The residue is dissolved in 50 ml. of hot 95% ethanol, treated with Norit[®], filtered, and allowed to cool. The yield of ethyl β -hydroxy- β,β -diphenylpropionate, obtained as colorless, needle-like crystals melting at 85–86°, is 40.5–45.5 g. (75–84%). The filtrate, on reduction in volume and cooling, yields small amounts of benzophenone, m.p. 46–47°.

2. Notes

1. This preparation may be accomplished by using one molecular equivalent of lithium amide; special reaction procedures must be employed, however, and the yields are not reproducible.² The preparation may also be accomplished (with reduced yield) by using sodium amide, but only under special reaction conditions.³

2. The lithium wire or ribbon is cut in about 0.25-g. pieces, stored under kerosene, and blotted with filter paper before addition.

3. Conversion is indicated by the discharge of the blue color.
4. Ethyl acetate and benzophenone as supplied by the Eastman Kodak Company were used without further purification.
5. The checkers added ether and permitted the ammonia to evaporate overnight. If a steam bath is employed, care must be exercised to prevent charring of the product.

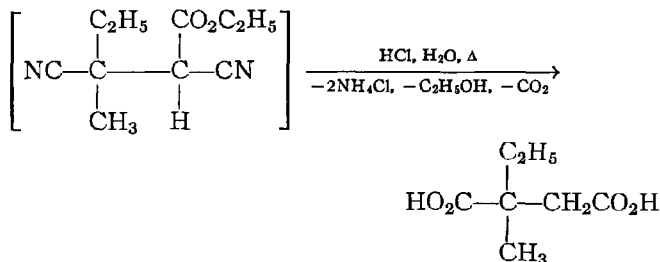
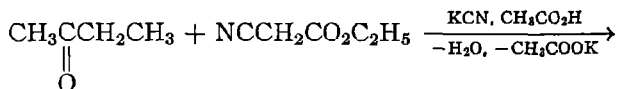
3. Methods of Preparation

This procedure is an adaptation of ones described by Dunnivant and Hauser.^{2,4} Ethyl β -hydroxy- β,β -diphenylpropionate has been prepared previously using the Reformatsky reaction by condensing ethyl α -bromoacetate with benzophenone by means of zinc metal.⁵

4. Merits of the Preparation

This procedure illustrates the use of lithio esters for the preparation of β -hydroxy esters. Isopropyl and *t*-butyl β -hydroxy- β,β -diphenylpropionate may be prepared in approximately 80% yields by using isopropyl or *t*-butyl acetates in place of ethyl acetate.² This procedure is generally more convenient than the Reformatsky reaction for the preparation of such esters. Under similar conditions ethyl acetate may conveniently be condensed with various aldehydes or ketones to give the corresponding β -hydroxy esters.⁴

1. Department of Chemistry, Duke University, Durham, North Carolina. This work was supported by the Army Research Office (Durham).
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α -ETHYL- α -METHYLSUCCINIC ACID(Succinic acid, α -ethyl- α -methyl-)

Submitted by F. S. PROUT, V. N. AGUILAR, F. H. GIRARD, D. D. LEE,
and J. P. SHOFFNER¹

Checked by WILLIAM G. DAUBEN and DALE L. WHALEN

1. Procedure

Potassium cyanide (71.6 g., 1.1 moles, U.S.P.) and 100 ml. of 95% ethanol are placed in a 2-l. round-bottomed flask having a ground joint and arranged with a Hershberg stirrer² (Note 1). A solution of 113 g. (106 ml., 1 mole) of ethyl cyanoacetate, 79 g. (98 ml., 1.1 moles) of 2-butanone, and 66 ml. of glacial acetic acid is added to the stirred solution over a period of 1 hour. The mixture is stirred for an additional hour, the stirrer is removed, and the mixture is allowed to stand at room temperature for 7 days (Note 2).

Concentrated hydrochloric acid (500 ml.) is added to the semi-solid reaction mixture, a reflux condenser is placed on the flask, and the mixture is heated under vigorous reflux for a period of 4 hours (Note 3). An additional 500 ml. of hydrochloric acid is added, and the boiling under reflux is continued for an additional 4 hours.

The cooled reaction mixture is extracted (Note 4) with four

portions of ether (400 ml., 250 ml., 200 ml., 200 ml.) (Note 5). The ether extracts are filtered and combined, and about two-thirds of the ether is distilled. The ethereal solution is transferred to a 500-ml. Erlenmeyer flask, and the remaining ether is removed. The residue (about 160 g.) is dissolved in 200 ml. of 24% hydrochloric acid (1 part water, 2 parts concentrated hydrochloric acid) and the solution distilled until the boiling point reaches 108° (Note 6). The solution is cooled and allowed to stand at 5° for about 20 hours. The product is collected by vacuum filtration and dried in a vacuum desiccator containing both concentrated sulfuric acid and potassium hydroxide pellets. The yield of α -ethyl- α -methylsuccinic acid is 65–75 g. (41–47%), m.p. 91–97°. Concentration of the mother liquor to 125 ml. gives an additional 8–9 g. of acid, m.p. 85–91° (Note 7).

2. Notes

1. The reaction can be run in an open flask because only a small amount of gas escapes. See Note 3. Sodium cyanide can be substituted for potassium cyanide if 2 g. of β -alanine is also employed as a catalyst.

2. Heating the reaction for shorter periods gave erratic results. At this point the semisolid mixture can be diluted with 200 ml. of water, extracted with benzene, and the benzene extract fractionally distilled to give ethyl 2,3-dicyano-3-methylpentanoate, b.p. 146.0–147.5° (2.5 mm.), n_D^{27} 1.4429 (highly purified ester has b.p. 138.5–141.5° (2 mm.), n_D^{25} 1.4432). The overall yield of α -ethyl- α -methylsuccinic acid is decreased by about 5% when the dicyano intermediate is isolated.

3. During the reflux period, gases are continuously evolved; these apparently are hydrogen chloride, carbon dioxide, ethyl acetate, and possibly ethyl chloride. The reaction should be run in a hood, or the gases should be trapped.³

4. If no layer separates on addition of the ether, add 200 ml. of water.

5. This extraction is designed to remove the organic acids from the inorganic salts. The extraction may also be effected by continuous extraction.⁴

6. The distillate consists of low-boiling solvents.

7. The acid can be purified further by dissolving 50 g. of it in 100 ml. of benzene. The solution is filtered, diluted with 100 ml. of hexane, and cooled to 5°. The yield of acid is 45.0 g., m.p. 97–102° (lit.⁵ m.p. 101–102°).

3. Methods of Preparation

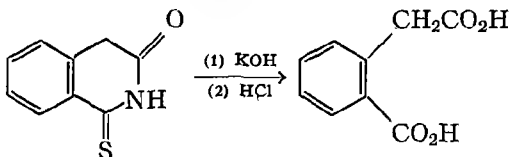
The one-step condensation to convert 2-butanone, ethyl cyanoacetate, and hydrocyanic acid to ethyl 2,3-dicyano-3-methylpentanoate is a modification of the procedure described by Smith and Horowitz⁵ in which pyridine acetate was employed as the catalyst. Higson and Thorpe⁶ employed a two-step procedure in which butanone was converted to its cyanohydrin, which in turn was condensed with ethyl cyanoacetate.

α -Ethyl- α -methylsuccinic acid also has been prepared by the sulfuric acid hydrolysis of ethyl α -ethyl- α -methyl- β -carbethoxysuccinate,⁷ the action of 80% sulfuric acid on 1-ethoxy-3-ethyl-3-methyl-1,2-cyclopropanedioic acid,⁸ and the dichromate oxidation of β -ethyl- β -methylbutyrolactone.⁹

4. Merits of the Preparation

This procedure illustrates a process which should be general for many α,α -disubstituted succinic acids. It is more convenient than those previously employed because the reaction sequence is carried out in one step.

1. Department of Chemistry, DePaul University, Chicago 14, Illinois.
2. See *Org. Syntheses*, Coll. Vol. **2**, 116 (1944).
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HOMOPHTHALIC ACIDSubmitted by P. A. S. SMITH and R. O. KAN¹

Checked by MELVIN S. NEWMAN and BERNARD DARRE

1. Procedure

Ten grams (0.056 mole) of 2a-thiohomophthalimide² and a solution of 30 g. of potassium hydroxide in 125 ml. of water are placed in a 300-ml., one-necked, round-bottomed flask (Note 1). The mixture is refluxed for 48 hours, filtered, and acidified with 12*N* hydrochloric acid. The solid that forms on cooling is collected by filtration and recrystallized from a mixture of 25 ml. of water and as much acetic acid (about 7 ml.) as necessary to dissolve the solid in the boiling solution, with addition of a little activated carbon. The yield of homophthalic acid, m.p. 181° (Note 2), is 6.1–7.5 g. (60–73%) (Note 3).

2. Notes

1. Because base can attack glass vessels, possibly introducing difficultly removable silicates into the reaction mixture, a copper flask is recommended for routine operations.

2. The melting point depends on the rate of heating. When the solid is heated slowly, the melting range can be as low as 172–174°.

3. An alternative procedure involves 3 days of refluxing in a mixture of 75 ml. of glacial acetic acid, 50 ml. of 12*N* hydrochloric acid, and 30 ml. of water. The product separates on cooling in a slightly lower yield (48%).

3. Methods of Preparation

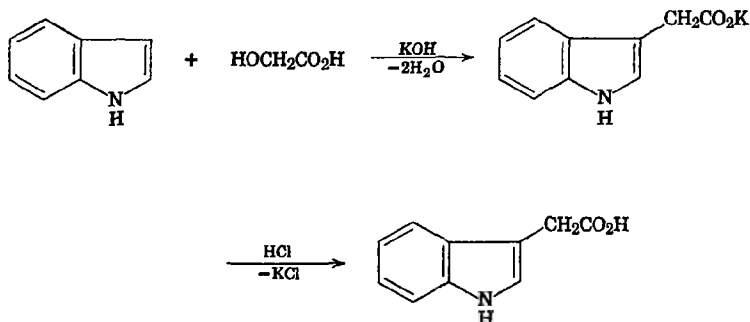
Homophthalic acid may be obtained by the oxidation of indene,^{3,4} the reduction of phthalonic acid,^{5,6} and the hydrolysis of *o*-carboxyphenylacetonitrile.⁷ Other methods are listed in an earlier volume.³

4. Merits of the Preparation

This is a general method for converting *2a*-thiohomophthalimides to homophthalic acids. Since *2a*-thiohomophthalimides are readily obtained from phenylacetyl chlorides,² this is a convenient method for preparing homophthalic acids.

1. Department of Chemistry, University of Michigan, Ann Arbor, Michigan.
2. P. A. S. Smith and R. O. Kan, this volume, p. 91.
3. O. Grummitt, R. Egan, and A. Buck, *Org. Syntheses*, Coll. Vol. **3**, 449 (1955).
4. W. F. Whitmore and R. C. Cooney, *J. Am. Chem. Soc.*, **66**, 1239 (1944).
5. K. Miescher and J. R. Billeter, *Helv. Chim. Acta*, **22**, 608 (1939).
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INDOLE-3-ACETIC ACID

Submitted by HERBERT E. JOHNSON and DONALD G. CROSBY¹

Checked by W. W. PRICHARD and B. C. MCKUSICK

1. Procedure

A 3-l. stainless steel, rocking autoclave (Note 1) is charged with 270 g. (4.1 moles) of 85% potassium hydroxide and 351 g. (3.00 moles) of indole (Note 2), and then 360 g. (3.3 moles) of 70% aqueous glycolic acid is added gradually (Note 3). The autoclave is closed and rocked at 250° for about 18 hours (Note 4). The reaction mixture is cooled to below 50°, 500 ml. of water is added, and the autoclave is rocked at 100° for 30 minutes to dissolve the potassium indole-3-acetate. The aqueous solution is cooled to 25° and removed from the autoclave, the autoclave is rinsed out well with water, and water is added until the total volume of solution is 3 l. The solution is extracted with 500 ml. of ether (Note 5). The aqueous phase is acidified at 20–30° with 12*N* hydrochloric acid and then is cooled to 10° (Note 6). The indole-3-acetic acid that precipitates is collected on a Büchner funnel, washed with copious amounts of cold water, and dried in air or a vacuum desiccator out of direct light (Note 7); weight 455–490 g. (87–93%); m.p. 163–165° (dec.).

The indole-3-acetic acid, which is cream-colored, is of high purity. If further purification is desired, it may be done con-

veniently by recrystallization from water. One liter of water is used for 30 g. of acid, with 10 g. of decolorizing carbon added. Recovery is about 22 g. of a nearly colorless product, m.p. 164–166° (dec.).

2. Notes

1. A stirred autoclave is just as satisfactory. The scale is not critical, for the checkers got equally good results on one-third the scale; they used a 1-l. rocking autoclave.

2. Indole from the Union Carbide Olefins Company, Institute, West Virginia, is satisfactory.

3. If the reactants are added in this order, with the glycolic acid being introduced over a 5–10 minute period, there is no violent heating because the heat of neutralization is used to melt the indole. An equivalent amount of anhydrous glycolic acid may be used, but this offers no special advantage.

4. These limits are not critical, but they are probably optimum. Reaction times of 24–30 hours are not particularly detrimental, and high yields of product can be obtained within 12 hours. The temperature can range from 230° to 270° with but slight effect on the yield of product.

5. This extraction may be omitted. It does, however, remove traces of neutral material and consequently gives a product with greater color stability.

6. This operation is most conveniently conducted in a flask equipped with a stirrer.

7. The product dries slowly, and several days in air or 24 hours in a vacuum desiccator is usually required. Considerable coloration will result if this is done in direct light. Drying in a heated oven or removing the water as a benzene azeotrope is not satisfactory because of some decarboxylation to skatole. The product should be stored in a dark bottle away from direct sunlight.

3. Methods of Preparation

Indole-3-acetic acid has been prepared by the Fischer indole synthesis,² by hydrolysis of indoleacetonitrile,³ from the reaction of gramine-type compounds with cyanide ion under conditions

which hydrolyze the nitrile,⁴ by the reaction of indole with ethyl diazoacetate followed by hydrolysis,⁵ through oxidation of indole-pyruvic acid,⁶ and by ultraviolet irradiation of tryptophan.⁷

4. Merits of the Preparation

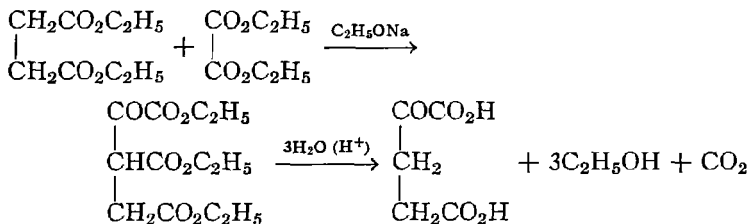
This is the most convenient method of preparing indole-3-acetic acid if an agitated autoclave is available. The method can be used to prepare other indole-3-acetic acids from α -hydroxy acids. For example, α -methylindole-3-acetic acid has been prepared by condensing indole with lactic acid.

Indole-3-acetic acid is a natural plant auxin and is used as a control in research on plant growth.

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α -KETOGLUTARIC ACID

(Glutaric acid, 2-oxo-)

Submitted by E. M. BOTTORFF and L. L. MOORE¹

Checked by WILLIAM G. DAUBEN and ROBERT M. COATES

1. Procedure

A. Triethyl oxalylsuccinate. In a 2-l. three-necked flask equipped with a sealed stirrer and a reflux condenser bearing a calcium chloride drying tube is placed 356 ml. (276 g., 6.00 moles) of anhydrous ethanol (Note 1). Sodium (23 g., 1.0 g. atom) is added in small portions at a rate sufficient to keep the ethanol boiling. External heating is required to dissolve the last portions of the metal. After all the sodium has dissolved, the excess ethanol is removed by distillation at atmospheric pressure; as the mixture becomes pasty, dry toluene is added in sufficient amounts to permit stirring and to prevent splattering of the salt. Distillation and addition of toluene is continued until all the ethanol is removed and the contents of the flask reach a temperature of 105° (Note 2). The sodium ethoxide slurry is cooled to room temperature and 650 ml. of anhydrous ether is added, followed by 146 g. (1.00 mole) of diethyl oxalate. To the yellow solution there is added 174 g. (1.00 mole) of diethyl succinate, and the mixture is allowed to stand at room temperature for at least 12 hours.

The mixture is hydrolyzed by the addition of 500 ml. of water

with stirring. The layers are separated, the ether layer is washed with 150 ml. of water, and the ether layer is discarded. The combined aqueous layers are acidified with 100 ml. of 12*N* hydrochloric acid, and the layers are separated. The aqueous layer is extracted with three 150-ml. portions of ether, which are added to the oily layer. The ethereal solution is dried over anhydrous magnesium sulfate, and the ether is removed by evaporation under water-pump pressure at a bath temperature of 35–45°. Triethyl oxalylsuccinate, a yellow oil weighing 235–250 g. (86–91%), remains in the flask (Note 3).

B. *α-Ketoglutaric acid*. A mixture of 225 g. (0.82 mole) of triethyl oxalylsuccinate, 330 ml. of 12*N* hydrochloric acid, and 660 ml. of water is heated under reflux for 4 hours, and the mixture is distilled to dryness under reduced pressure at a bath temperature of 60–70° (Note 4). The liquid residue, which solidifies readily on standing, is warmed with 200 ml. of nitroethane on a steam bath until it is in solution. The warm solution is filtered, the funnel is washed with 40 ml. of nitroethane, and the filtrate is stirred at 0–10° for 5 hours. *α-Ketoglutaric acid* is separated by filtration and dried at 90° under reduced pressure for 4 hours. It is obtained as a tan solid; weight 88–99 g. (73–83%); m.p. 103–110° (Note 5).

2. Notes

1. Commercial absolute ethanol is dried by heating with sodium and diethyl succinate and is then distilled directly into the reaction flask.

2. If the toluene method to remove all the ethanol is not used, the yield is lower by 5–10%.

3. Triethyl oxalylsuccinate begins to decompose at 84° at 760 mm. It cannot be distilled without decomposition even at a pressure of 1 mm.

4. The color of the *α*-ketoglutaric acid is darker if the pot temperature goes much above 90° during the evaporation and recrystallization.

5. The product is pure enough for most purposes. Further recrystallization from nitroethane does not improve the melting point.

3. Methods of Preparation

The present procedure is a modification of one reported in an earlier volume of *Organic Syntheses*.² The methods used to prepare triethyl oxalysuccinate and α -ketoglutaric acid are summarized in that volume.

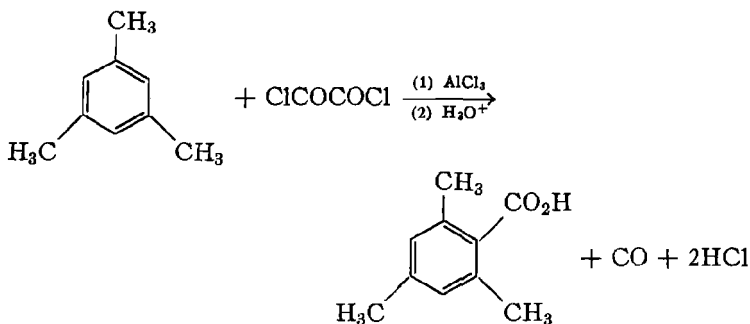
4. Merits of the Preparation

The advantages of this procedure over the earlier version are the use of sodium ethoxide instead of potassium ethoxide and better reproducibility.

1. Organic Chemical Development, Eli Lilly and Company, Indianapolis, Indiana.
2. L. Friedman and E. Kosower, *Org. Syntheses*, Coll. Vol. **3**, 510 (1955).

MESITOIC ACID

(Benzoic acid, 2,4,6-trimethyl-)



Submitted by PHILLIP E. SOKOL¹

Checked by MELVIN S. NEWMAN and VERN G. DEVRIES

1. Procedure

Caution! The reaction should be carried out in a hood because carbon monoxide is evolved.

The apparatus consists of a 2-l. three-necked flask fitted with a

sealed stirrer, a 500-ml. addition funnel, and a condenser protected by a drying tube connected to an alkaline trap. In it are placed 146 g. (1.10 moles) of anhydrous aluminum chloride (Note 1) and 700 ml. of dry carbon disulfide. The suspension is cooled to 10–15° in an ice bath, and 139 g. (1.10 moles) of oxalyl chloride (Note 2) is added dropwise with stirring over a 30-minute period. After this addition the reaction mixture is stirred for 15 minutes. A solution of 120 g. (1.00 mole) of mesitylene (Note 3) in 200 ml. of dry carbon disulfide is added dropwise with stirring over a 1-hour period to the mixture, the temperature being maintained at 10–15°. Hydrogen chloride evolution is observed after about 5 minutes, and a red complex soon forms.

After the addition is completed, the reaction mixture is refluxed for 1 hour and is then poured very cautiously with manual stirring onto a mixture of 2 kg. of crushed ice and 300 ml. of 12*N* hydrochloric acid in a 4-l. beaker. The mixture thus formed is extracted with three 250-ml. portions of carbon tetrachloride. The combined organic extracts are washed with two 500-ml. portions of water, and the acid is then extracted with 500 ml. of ice-cold 10% sodium hydroxide solution. The aqueous extract is then slowly added to 250 ml. of 6*N* hydrochloric acid. The suspension is cooled, and the mesitoic acid is separated by filtration, washed thoroughly with water, and dried. The colorless crude acid (m.p. 149–150°) weighs 106–124 g. (65–76%) (Note 4) and is sufficiently pure for most purposes (Note 5).

2. Notes

1. Good results have been obtained with several different varieties of anhydrous aluminum chloride.

2. High-purity commercial oxalyl chloride was used without further purification.

3. Commercial mesitylene of high purity (99+%) was used.

4. Similar yields were obtained when experiments were run on a 0.10-mole scale.

5. For recrystallization, 10 g. of crude acid is dissolved in 20 ml. of 45% methanol at reflux. About 9.5 g. of mesitoic acid, m.p. 153–154° (uncor.),² is obtained.

3. Methods of Preparation

Mesitoic acid has been prepared by carbonation of mesityl-magnesium bromide; ²⁻⁴ by hydrolysis of its amide prepared by condensation of mesitylene with carbamyl chloride under the influence of aluminum chloride; ⁵ by oxidation of isodurene with dilute nitric acid; ^{6,7} by distillation of 2,4,6-trimethylmandelic acid (low yield); ⁸ by dry distillation of 2,4,6-trimethylphenylglyoxylic acid; ⁹ by oxidation of the latter with potassium permanganate; ¹⁰ and by treating 2,4,6-trimethylphenylglyoxylic acid with concentrated sulfuric acid in the cold ¹¹ or with heating. ¹²

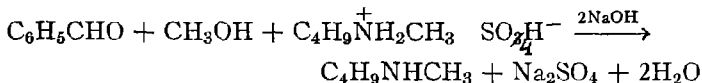
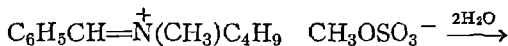
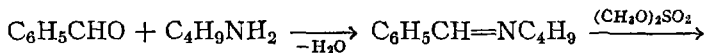
4. Merits of the Preparation

The method described in this preparation of mesitoic acid avoids the preparation of bromomesitylene, ¹³ and the yield of acid is essentially the same as that from the two-step synthesis. ^{2,13} This procedure appears to be general and can be used to prepare such acids as α - and β -naphthoic acids, ¹⁴ cumenecarboxylic acid, 2,5-dimethylbenzoic acid, and durenecarboxylic acid. Carboxylic acids could not be obtained from benzothiophene, veratrole, *p*-dimethoxybenzene, and ferrocene under the conditions of this reaction. Although there has been no exhaustive study, this procedure is probably applicable to a variety of aromatic compounds, especially alkylated aromatics. Aromatic compounds which readily undergo oxidation, e.g., ferrocene, catechol, and hydroquinone, do not lend themselves to this method.

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N-METHYLBUTYLAMINE

(Butylamine, N-methyl-)

Submitted by JOHN J. LUCIER, ARLO D. HARRIS, and PHILIP S. KOROSCEC¹

Checked by MAX TISHLER and M. BENNETT.

1. Procedure

A 1-l. round-bottomed flask fitted with a reflux condenser bearing a soda-lime drying tube is successively charged with 100 ml. of anhydrous benzene, 36.6 g. (0.50 mole) of *n*-butylamine, and 63.7 g. (61 ml., 0.60 mole) of benzaldehyde (Note 1). The mixture is heated under reflux for 30 minutes (Note 2). The condenser is replaced by a Claisen distillation head, and the mixture is distilled until the temperature reaches 100° (Note 3). The residue, which is mostly N-benzylidenebutylamine, is cooled, and the distillation head is replaced by the reflux condenser bearing a soda-lime drying tube.

A solution of 75.6 g. (57 ml., 0.60 mole) of dimethyl sulfate (*Toxic!* Note 4) in 200 ml. of anhydrous benzene is added through the condenser with intermittent swirling (Note 2). The mixture is then heated *gently*. After a short period (about 10 minutes) the reaction becomes mildly vigorous, and the heating is stopped (Note 5). The ebullition subsides after about 10 minutes. The mixture is heated under reflux for 30 minutes. It is then steam-distilled until the distillate becomes clear; about 500 ml. of distillate is collected (Note 6). The residue is cooled in an ice bath, and 60 g. (1.5 moles) of sodium hydroxide is added with continuous swirling. The layers are separated, and the amine

layer is dried for several hours over 5 g. of sodium hydroxide. The amine layer is separated, dried over a second 5-g. portion of sodium hydroxide (Note 7), and distilled from a 50-ml. Claisen flask containing 2 g. of sodium hydroxide. N-Methylbutylamine is collected at 86–90°(745 mm.); weight 19.6–23.0 g. (45–53%); n^{20}_D 1.4010–1.4020. The product contains 3–5% of impurity according to vapor-phase chromatographic analysis.

2. Notes

1. The benzaldehyde and *n*-butylamine were obtained from the Eastman Kodak Company (white label grade). The benzaldehyde was used without further purification. The *n*-butylamine was redistilled before use.

The checkers dried benzene over sodium-lead alloy (dri-Na, Baker). Its water content was less than 0.1 mg. per ml. by Karl Fischer titration.

2. The checkers stirred the mixture with a magnetic stirrer.

3. This distillation is carried out to remove the water formed by the first reaction. No more water comes over after the temperature reaches 100°. Toward the end of distillation, slight bumping may occur.

4. The dimethyl sulfate was purchased from Matheson, Coleman and Bell and was used without further purification. Both the liquid and the vapors of dimethyl sulfate are *toxic*, and the compound must be handled with care.

5. An ice bath should be kept ready to restrain the reaction if necessary.

6. In a simpler alternative to steam distillation, 200 ml. of water is added to the benzene solution, and the mixture is vigorously stirred under gentle reflux for 20 minutes. The mixture is cooled to room temperature. The aqueous layer is separated, extracted with 100 ml. of ether to remove traces of benzaldehyde, and then treated with 60 g. of sodium hydroxide as in the present procedure.²

7. If a larger portion of sodium hydroxide is used, a semisolid mass is formed from which the product can be separated only with difficulty.

3. Methods of Preparation

Unsymmetrical secondary aliphatic amines have been prepared by reaction of alkyl halides with benzyldene amines and subsequent hydrolysis;^{3,4} by reaction of alkyl halides with alkyl amines;⁵ by reduction of amine-aldehyde adducts;⁶⁻⁸ and by dealkylation of tertiary amines with dibenzoyl peroxide.⁹

In the present procedure, the method of Decker and Becker³ has been modified by substitution of a dialkyl sulfate for the corresponding alkyl halide.

4. Merits of the Preparation

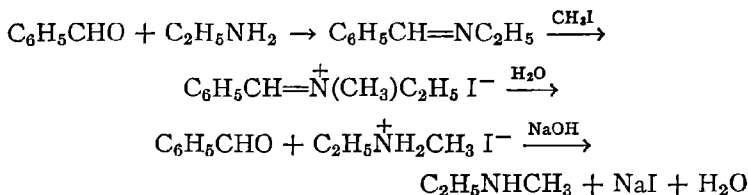
The procedure is a general one for the preparation of unsymmetrical aliphatic amines, for the submitters have used it to obtain good yields of N-methylpentylamine, N-methylhexylamine, N-methylheptylamine, N-ethylbutylamine, N-ethylpentylamine, and N-ethylheptylamine.

Compared to the procedure of Decker and Becker³ and that of Wawzonek, McKillip, and Peterson in this volume,⁴ the present procedure has the advantages of being simpler and using cheaper alkylating agents. It tends to give lower yields and less pure products than the procedure of Wawzonek, McKillip, and Peterson.

1. Department of Chemistry, University of Dayton, Dayton, Ohio. This work was supported by Wright Air Development Division of the United States Air Force, Air Research and Development Command, under Contract No. AF 35(616)-6607.
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N-METHYLETHYLAMINE

(Ethylamine, N-methyl-)

Submitted by S. WAWZONEK, W. MCKILLIP, and C. J. PETERSON¹Checked by J. K. WILLIAMS, H. E. WINBERG, C. L. DICKINSON,
and B. C. MCKUSICK

1. Procedure

A. *N-Benzylideneethylamine*. Benzaldehyde (466 g., 4.40 moles) is placed in a 2-l. three-necked flask equipped with a mechanical stirrer and a thermometer. The flask is cooled to 5° in an ice bath, and 200 g. (4.44 moles) of anhydrous ethylamine (Note 1) is added to the stirred benzaldehyde at such a rate that the temperature remains below 15°; about 50 minutes is required for the addition. The mixture is stirred for an additional 30 minutes at room temperature and allowed to stand for 1 hour.

The condenser is arranged for downward distillation, and the water is removed from the product by codistillation with 200 ml. of benzene. The residue, *N*-benzylideneethylamine, is purified by distillation through a 25-cm. Fenske column; b.p. 52–53° (4.5 mm.); n_D^{23} 1.5400; weight 470–523 g. (80–89%) (Note 2).

B. *N-Methylethylamine*. *N*-Benzylideneethylamine (133 g., 1.00 mole) is heated with 156 g. (1.10 moles) of methyl iodide (Note 3) in a 300-ml. pressure bomb at 100° for 24 hours (Note 4). The bomb is cooled to 50° (Note 5), and the dark, viscous oil is poured into a 1-l. beaker containing 200 ml. of water. The bomb is rinsed with three 50-ml. portions of water, and the washings are combined with the main solution. The resulting mixture is heated with manual stirring on a steam bath for 20 minutes

and then cooled in an ice bath to room temperature. The resulting mixture is extracted with two 75-ml. portions of ether (Note 6). The ether layer is washed with two 50-ml. portions of water, and the washings are combined with the main aqueous layer, which is then heated at 100° on a steam bath for 20 minutes to remove traces of ether.

For the liberation of N-methylethylamine, a 1-l. Claisen flask is equipped with a 250-ml. separatory funnel and an efficient condenser for distillation. The receiver is cooled with a mixture of acetone and dry ice (Note 7). A solution of 100 g. (2.5 moles) of sodium hydroxide in 100 ml. of water is added to the flask and kept at about 100° by heating on a steam bath. The aqueous solution of N-methylethylamine hydriodide is added to this solution through the separatory funnel in the course of 1.5 hours. After the addition is complete, the final solution is heated for an additional 30 minutes. Crude N-methylethylamine, b.p. 30–70°, collects in the cooled receiver. It is purified by distillation from 25 g. of solid potassium hydroxide in a 250-ml. modified Claisen flask fitted with a 25-cm. Fenske column and a receiver cooled by dry ice and acetone. N-Methylethylamine is collected at 34–35°; weight 49–55 g. (83–93%); n_D^{25} 1.3830.

2. Notes

1. The ethylamine is cooled to 5° to prevent loss by evaporation. Addition is made directly from the bottle with intermittent cooling in an ice bath.

2. The aldimine need not be distilled but can be used directly in the next step.

3. Dimethyl sulfate, when substituted for the methyl iodide, reacts vigorously with the aldimine at ice-bath temperatures and gives a 49% yield of N-methylethylamine together with considerable tar.

4. Four times these amounts have been used for N-methylbutylamine with equal success.

5. The pressure bomb is opened while still warm (50°). If the bomb is allowed to cool below this temperature, the product solidifies and removal becomes a problem.

6. The benzaldehyde may be recovered after removal of the ether.

7. Because of the low boiling point of N-methylethylamine, there must be efficient cooling or a portion of the product will be lost.

3. Methods of Preparation

This procedure is a modification of the method used for N-methylallylamine.²

N-Methylethylamine has been prepared by heating ethylamine with methyl iodide in alcohol at 100°;³ by the hydrolysis of N-methyl-N-ethylarenesulfonamides,^{4,5} *p*-nitroso-N-methyl-N-ethylaniline,⁶ or methylethylbenzhydrylidene ammonium iodide;⁷ by catalytic hydrogenation of ethyl isocyanate or ethyl isocyanide;⁸ and by the reduction of ethyl isocyanate by lithium aluminum hydride,⁹ of N-methylacetisoaldoxime by sodium amalgam and acetic acid,¹⁰ or of a nitromethane/ethylmagnesium bromide adduct by zinc and hydrochloric acid.¹¹

4. Merits of the Preparation

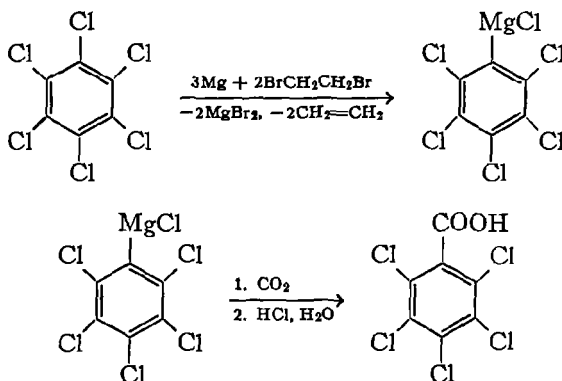
This preparation illustrates a general method for the synthesis of N-methylalkylamines. The submitters have used it to prepare N-methylbutylamine (Note 4) and N-methylallylamine, and the checkers have used it to prepare N-methylisopropylamine (80%), N-methylisobutylamine (67%), N-methyl-*tert*-butylamine (52%), and N-methyl-2-methoxyethylamine (55%). Secondary amines are useful as starting materials for the synthesis of 1,1-disubstituted hydrazines and asymmetric amine imides.

The method gives better yields, utilizes more readily available starting materials, and is much less laborious than the hydrolysis of N-methyl-N-alkylarenesulfonamides and *p*-nitroso-N, N-di-alkylanilines, or the lithium aluminum hydride reduction of alkyl isocyanates. Compared to the closely related procedure of Lucier, Harris, and Korosec,¹² in which the N-benzylidenealkylamine is treated with dialkyl sulfate at atmospheric pressure, the present procedure tends to give higher yields and purer products, but it is less convenient because of the need for a pressure vessel.

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PENTACHLOROBENZOIC ACID

(Benzoic acid, pentachloro-)



Submitted by D. E. PEARSON and DOROTHA COWAN¹

Checked by VIRGIL BOEKELHEIDE and FRED G. H. LEE

1. Procedure

Magnesium turnings (39 g., 1.6 g. atoms) and hexachlorobenzene (142.4 g., 0.5 mole, m.p. 228–229°) in 1 l. of dry ether are brought to gentle reflux in a 3-l. three-necked flask heated by a Glascol[®] mantle at 20 volts (Note 1). Ethylene bromide (188 g., 1.0 mole) in 200 ml. of dry benzene is added through a Hersh-

berg funnel ² over a period of 48 hours (about 1 drop/25 seconds) (Note 2). Efficient stirring is maintained throughout the period of addition, during which the reaction mixture turns dark brown and forms a precipitate. The mixture is cooled to room temperature, and carbon dioxide, generated from dry ice and dried by passage through anhydrous calcium chloride, is added under the surface of the stirred mixture for at least 3 hours and at such a rate as to minimize clogging of the entrance tube (Note 3). After this addition 10% aqueous hydrochloric acid is added slowly until the mixture is strongly acid. The ether and benzene are removed by distillation, and the crude pentachlorobenzoic acid left in the water is removed by filtration and is washed free of salts with water. The dark-brown damp acid is converted to the ammonium salt by repeated extraction with hot dilute ammonium hydroxide (1 part by volume of concentrated ammonium hydroxide and 2 parts of water) followed by decantation. The combined decanted solutions are treated with Norit[®] while still hot, filtered, and then strongly acidified while still hot with concentrated hydrochloric acid. The precipitated acid is digested for at least several hours (Note 4). After the suspension has been cooled, the crude brown-colored acid is removed by filtration, washed with cold water, and air-dried to give 113 g. (77%) of product. The crude acid is recrystallized from 900 ml. of 50% aqueous methanol to yield 95 g. (65%) of tan-colored needles, m.p. 202–206° (Note 5).

2. Notes

1. The atomic proportions of magnesium are not related to the mole quantity of hexachlorobenzene in this or any other entrainment reaction. The excess magnesium (1.1 g. atoms in this case) is used to react with ethylene bromide and leave 0.5 g. atom of clean-surfaced magnesium. Ordinarily 1 mole of entrainment reagent is used per mole of "inert" halide, but for this preparation 2 moles of entrainment reagent per mole of halide gives a better yield.

2. Little attention is needed provided that the capillary tube is fitted properly. The capillary tube of the Hershberg dropping

funnel should be about 4.5 in. long, and a Band S 24 platinum wire should be inserted to fit very snugly.

3. A T-tube in the carbon dioxide stream serves to bypass the gas if its rate of addition is too rapid. Also, the T-tube is large enough to permit the insertion of a plunger to dislodge particles within the mouth of the tube.

4. Without digestion the acid will contain appreciable amounts of the ammonium salt. In an alternative method of purification the crude acid is converted to the insoluble sodium salt. The sodium salt can be recrystallized from 95% ethanol to give flaky white crystals, m.p. 339–340°. Digestion of the sodium salt with 1 part of concentrated hydrochloric acid and 1 part of water yields the free acid. From 10 g. of crude acid, 7.3 g. of purified acid can be obtained from the sodium salt. The free acid is reported to crystallize well from toluene and light petroleum ether.³

5. The melting point is reported variously in the range from 199° to 208°. The acid is colorless if purified by conversions through the sodium salt (Note 4), but the yield is lower.

3. Methods of Preparation

Pentachlorobenzoic acid has been prepared by oxidation of pentachlorotoluene with nitric acid and mercury,³ by oxidation of pentachlorobenzaldehyde by potassium permanganate,⁵ and by chlorination of tetrachlorophthalyl chloride⁶ and of dichlorobenzoic acids.⁷ Pentachlorobenzoic acid recently has been prepared by the exhaustive chlorination of benzoic acid in sulfuric acid containing iodine.⁸ The present procedure has been adapted from that of Pearson, Cowan, and Beckler.⁹

4. Merits of the Preparation

Ethylene bromide has been demonstrated to be as efficient as ethyl bromide as an entrainment agent.⁹ Its use is advantageous because a second Grignard reagent is not introduced in the reaction mixture—only magnesium bromide. An additional feature of this preparation and of most preparations involving entrainment agents is the slow rate of addition of the entrainer, which

permits adequate time for the "inert" halide (in this preparation, hexachlorobenzene) to react on the bright, clean surfaces of the magnesium turnings.

Although pentachlorophenylmagnesium chloride can be made in tetrahydrofuran without the use of the entrainment method, the Grignard reagent in this solvent does not react with carbon dioxide to give pentachlorobenzoic acid in good yield.¹⁰

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PERBENZOIC ACID

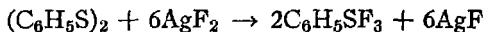
WARNING

It has been reported that the evaporation of a chloroform solution of peroxybenzoic acid (perbenzoic acid) according to the directions published in this series¹ has resulted in a heavy explosion. Hence suitable precautions should be observed in carrying out solvent evaporations from solutions of peroxybenzoic acid. Such precautions and other useful information have been given elsewhere in this series.²

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PHENYLSULFUR TRIFLUORIDE

(Benzenesulphenyl trifluoride)

Submitted by WILLIAM A. SHEPPARD¹

Checked by E. S. GLAZER and JOHN D. ROBERTS

1. Procedure

Caution! Phenylsulfur trifluoride and by-products (e.g., hydrogen fluoride from hydrolysis) are toxic, and all manipulations should be carried out in a good hood. Silver difluoride is a powerful oxidative fluorinating agent and reacts vigorously with many organic materials. These reagents should not be allowed to come in contact with the skin.

A 1-l., four-necked, round-bottomed flask equipped with reflux condenser, sealed stirrer, thermometer, and solid addition funnel² and protected from atmospheric moisture with a Drierite[®] guard tube is carefully dried and flushed with a dry inert gas (Note 1). The flask is charged with 453 g. (3.1 moles) of silver difluoride (Note 2) and 500 ml. of 1,1,2-trichloro-1,2,2-trifluoroethane (Note 3), and phenyl disulfide (100 g., 0.458 mole) (Note 4) is weighed into the solid addition funnel. The stirrer is started, and phenyl disulfide is added to the slurry in small portions. An exothermic reaction occurs, and after the addition of several portions the reaction mixture reaches a temperature of 40° (Note 5). By intermittent use of a cooling bath and by adjusting the rate of addition of the disulfide, the reaction temperature may be maintained between 35° and 40°. The addition of the phenyl disulfide requires 45–60 minutes. On completion of the addition the suspension of black silver difluoride has been converted to yellow silver monofluoride, and the exothermic reaction gradually subsides. The reaction mixture is stirred for an additional 15–30 minutes without external cooling and then quickly heated to reflux.

The reaction mixture is filtered hot through a fluted filter paper

under a blanket of dry nitrogen into a dry, 1-l., round-bottomed flask. The residue of solid silver fluoride is washed with a total of 500 ml. of boiling 1,1,2-trichloro-1,2,2-trifluoroethane in portions (Note 6). The filtrates are combined and distilled through a short Vigreux column, an oil bath not heated over 70° being used (Note 7). The residue of phenylsulfur trifluoride is transferred to a 200-ml. round-bottomed flask and distilled, b.p. 47–48° (2.6 mm.), through a Claisen-type distillation column, discarding a small fore-run. The product is obtained in a yield of 84–92 g. (55–60%) as a colorless liquid, m.p. –10° (Note 8). Since phenylsulfur trifluoride slowly attacks Pyrex® glass, it should be used immediately. It can be stored for several days in glass at –80° or in polyethylene, however, and may be stored indefinitely at room temperature in bottles of Teflon® polytetrafluoroethylene resin or aluminum (Note 9).

2. Notes

1. The equipment should be dried carefully by the techniques normally employed when preparing for a Grignard reaction. Dry nitrogen gas was normally employed to flush the apparatus, but any dry inert atmosphere, or dry air, could be employed.

2. A technical grade of silver difluoride (approximately 85%) is available from Harshaw Chemical Company. Better grades of silver difluoride are available and may be employed. It is important that the silver difluoride be a black powder. If the material is light brown and lumpy, a lower yield of product may be obtained. Normally, the contents of a 1-lb. can (approximately 435–470 g.) are employed.

3. 1,1,2-Trichloro-1,2,2-trifluoroethane (trademark "Freon-113"), b.p. 47°, is available from the Organic Chemicals Department, E. I. du Pont de Nemours and Company, Wilmington, Delaware.

4. Eastman's white label grade phenyl disulfide is suitable.

5. Caution must be exercised in the addition of the phenyl disulfide. There is a short induction period between the addition of disulfide and the exothermic reaction. If the disulfide is added too rapidly, a vigorous exothermic reaction, which is difficult to

control, will result. The extensive use of a cooling bath should be avoided because the reaction rate is sufficiently slow at lower temperatures to allow buildup of reactants and the development of a vigorous, uncontrollable reaction.

6. Etching of the glass equipment is reduced to a minimum if all equipment used in the preparation and subsequent manipulation is rinsed with water and acetone *immediately* after use.

7. The Freon[®] solvent may be removed under reduced pressure in order to shorten the distillation time. Since phenylsulfur trifluoride attacks glass, the total time involved in the preparation and distillation in the glass equipment should be kept to a maximum of a few hours. It is recommended that the column be changed after distillation of the Freon[®]. If the preparation cannot be completed within a day, the Freon[®] solution of crude phenylsulfur trifluoride may be stored in polyethylene bottles overnight.

8. In contact with moisture of glass, phenylsulfur trifluoride develops pink, green, or bluish colors. A small amount of discoloration does not appear to affect the quality. Phenylsulfur trifluoride prepared in glass equipment always contains a few percent of phenylsulfinyl fluoride. The amount of this impurity depends on the care taken to exclude moisture during preparation and manipulation.

9. Phenylsulfur trifluoride slowly oozes through polyethylene bottles after storage for several days. However, a sample of phenylsulfur trifluoride has been stored in a bottle of Teflon[®] for several years without decomposition. Storage in a dry atmosphere in a well-ventilated area is recommended.

3. Methods of Preparation

Phenylsulfur trifluoride has been prepared only by the present method.^{3,4}

4. Merits of the Preparation

This procedure illustrates a fairly general method for the preparation of alkyl- and arylsulfur trifluorides. The method has also been applied to the synthesis of nitrophenyl-, tolyl-,

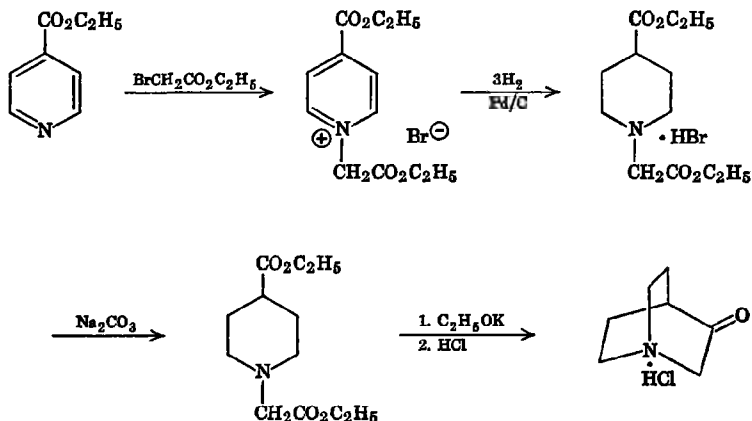
and fluorobutylsulfur trifluorides,^{3,4} and it is probably applicable to any disulfide that does not contain groups reactive with silver difluoride. 2,4-Dinitrophenyl- and perfluoroalkylsulfur trifluorides have been prepared by reaction of disulfides with fluorine or by electrolytic fluorination.^{5,6} These other routes to sulfur trifluoride compounds are not general or convenient, and they often give low yields.

The sulfur trifluoride compounds are useful as selective agents for conversion of carbonyl and carboxyl groups to difluoromethylene⁷ and trifluoromethyl groups,^{3,4} respectively, and as intermediates for synthesis of arylsulfur pentafluorides.^{3,8}

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3-QUINUCLIDONE HYDROCHLORIDE

(3-Quinuclidinone, hydrochloride)

Submitted by H. U. DAENIKER and C. A. GROB¹Checked by E. CIGANEK, W. R. HERTLER, A. D. JOSEY,
and B. C. MCKUSICK

1. Procedure

A. *1-Carbethoxymethyl-4-carbethoxypyridinium bromide*. A solution of 151 g. (1.00 mole) of ethyl isonicotinate (Note 1) and 167 g. (1.00 mole) of ethyl bromoacetate in 500 ml. of ethanol is allowed to stand overnight at room temperature in a 1-l. round-bottomed flask equipped with a reflux condenser (Note 2). The mixture is then heated at the reflux temperature for 4 hours. The resulting solution of 1-carbethoxymethyl-4-carbethoxypyridinium bromide is used directly for the next step (Note 3).

B. *1-Carbethoxymethyl-4-carbethoxypiperidine*. Fifteen grams of 10% palladium on charcoal² is added to the solution of the pyridinium bromide. The mixture is placed in an agitated 2-l. hydrogenation autoclave and hydrogenated at 90° under an initial pressure of 100 atm. (Note 4). Slightly more than the calcu-

lated amount of hydrogen (3 moles) is absorbed within 30–60 minutes. The mixture is cooled to 25°, and the catalyst is separated by filtration and washed with 100 ml. of ethanol. The filtrate is evaporated to dryness under water-aspirator vacuum at a bath temperature of 50–60°. The residue, semicrystalline 1-carbethoxymethyl-4-carbethoxypiperidine hydrobromide, is taken up in 500 ml. of ice-cold water. The solution is added to 500 ml. of chloroform in a 5-l. beaker immersed in an ice bath, and an ice-cold solution of 150 g. of potassium carbonate in 250 ml. of water is added gradually with stirring (Note 5). After the carbon dioxide evolution has subsided, the mixture is placed in a 2-l. separatory funnel and thoroughly shaken for some time. The lower, organic layer is drawn off and washed once with 200 ml. of water. The aqueous layers are combined and washed once with 500 ml. of chloroform. The two chloroform extracts are combined and dried over anhydrous sodium sulfate. After 1 hour the sodium sulfate is separated on a Büchner funnel and washed with two 200-ml. portions of chloroform. The chloroform is removed on a steam bath, and the resulting oily residue is distilled under high vacuum through a 20-cm. Vigreux column. A fore-run, weight 4–8 g., is collected below 110° (0.20 mm.). Then 156–190 g. (64–78%) of 1-carbethoxymethyl-4-carbethoxypiperidine is collected as a colorless oil, b.p. 111–113° (0.2 mm.), d_{4}^{25} 1.057, n_D^{20} 1.4585.

C. *3-Quinuclidone hydrochloride*. A 2-l. three-necked flask is fitted with a Hershberg stirrer, a pressure-equalizing addition funnel, and a condenser connected to a source of dry nitrogen. Absolute toluene (330 ml.) and 80 g. (2.05 g. atom) of potassium free of oxide crust are added. (*Caution! Directions² for the safe handling of potassium should be consulted.*) The air in the flask is replaced by an atmosphere of dry nitrogen that is maintained until the reaction mixture is decomposed. The flask is heated in an oil bath until the toluene begins to reflux gently. As soon as the potassium is molten, it is pulverized by vigorous stirring. One hundred twenty-five milliliters (98.6 g., 2.14 moles) of absolute ethanol (Note 6) is added through the addition funnel within 30 minutes while heating and stirring are continued. After disappearance of the potassium the temperature is raised to 130°, and

a solution of 200 g. (0.822 mole) of 1-carbethoxymethyl-4-carboethoxypiperidine in 500 ml. of absolute toluene is added within 2 hours. The mixture is stirred and heated for an additional 3 hours.

The resulting solution is cooled to 0° and decomposed by careful addition of 500 ml. of 10*N* hydrochloric acid. The mixture is transferred to a separatory funnel, the aqueous phase is separated, and the toluene layer is extracted with two 250-ml. portions of 10*N* hydrochloric acid. The aqueous extracts are combined and heated under reflux for 15 hours to effect decarboxylation. The hot, dark-colored solution is treated with 10 g. of activated charcoal, filtered, and evaporated to dryness under reduced pressure. The residue is washed into a separatory funnel with 300 ml. of water. The solution is treated with saturated aqueous potassium carbonate solution until it is alkaline to litmus; the carbonate solution must be added very carefully to prevent excessive foaming. Solid potassium carbonate is added until a thin slurry is obtained, and the slurry is extracted with four 400-ml. portions of ether. The combined ether extracts are dried for at least 60 minutes over calcined potassium carbonate and then filtered.

The ether is removed by distillation on a steam bath through a column filled with Raschig rings. The yellowish crystalline residue is treated with 150 g. of ice and 150 g. (130 ml.) of 10*N* hydrochloric acid, and the solution is evaporated to dryness under reduced pressure (Note 7). The crystalline residue is dissolved in the minimum amount of hot water (about 70 ml.), and boiling isopropyl alcohol (about 1.5 l.) is added until crystalline 3-quinuclidone hydrochloride begins to separate. The mixture is cooled to 0–5°, and the solid is separated by filtration, washed with acetone, and dried. The yield of 3-quinuclidone hydrochloride, m.p. 294–296° (sealed capillary) (Note 8), is 102–109 g. (77–82%).

2. Notes

1. The checkers used ethyl isonicotinate purchased from K and K Laboratories, Inc., Jamaica, New York, or prepared by esterification of isonicotinic acid as described by La Forge ⁴ for nicotinic acid.

2. The quaternization is slightly exothermic.
3. The quaternary salt may be isolated by evaporation of the solution and subsequent recrystallization of the residue from isopropyl alcohol; m.p. 159° (dec.). Calcd. for $C_{12}H_{18}BrNO_4$: C, 45.30; H, 5.07; Br, 25.12. Found: C, 45.41; H, 5.14; Br, 25.28.
4. The checkers found that hydrogenation proceeded rapidly and quite exothermically at a pressure of only 7 atm. at 90°. They used 10% palladium-on-carbon powder purchased from Engelhard Industries Inc., Newark, New Jersey.
5. The evolution of carbon dioxide causes considerable foaming. Losses are easily avoided if a 5-l. beaker is used.
6. Commercial absolute alcohol was further dried by treatment with magnesium and a little iodine with subsequent redistillation, as described by Lund and Bjerrum.⁵
7. In an alternative method of isolating crude quinuclidone hydrochloride, found by the checkers to give equally good results, the dried ether solution of quinuclidone is transferred to a 2-l. round-bottomed flask equipped with a stirrer, a gas-inlet tube, and a gas-exit tube. The flask is immersed in an ice bath, and gaseous hydrogen chloride is passed into the stirred solution until it begins to bubble out, indicating that the solution is saturated. The quinuclidone hydrochloride that precipitates is collected on a Büchner funnel, washed with acetone, and dried in a vacuum desiccator. The product is then dissolved in hot water and precipitated with isopropyl alcohol as described in the procedure.
8. The melting point depends on the rate of heating and the apparatus used. The checkers observed m.p. 297–305°, 298–303°, and 301° under various conditions.

3. Methods of Preparation

Quinuclidone hydrochloride has been prepared by intramolecular condensation of 1-carbethoxymethyl-4-carbethoxypiperidine with potassium⁶⁻⁸ or, as in the present procedure, with potassium ethoxide.⁹ 1-Carbethoxymethyl-4-carbethoxypiperidine has been prepared by alkylating ethyl hexahydroisonicotinate with ethyl chloroacetate^{6,8} or by the present method.⁷

4. Merits of the Preparation

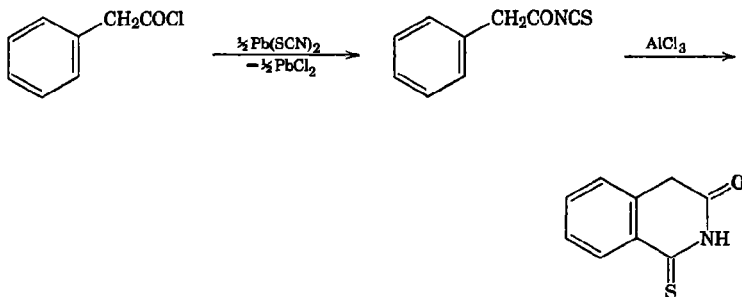
This is the most convenient way to prepare quinuclidone hydrochloride. The second step illustrates the conversion of an N-alkylpyridinium salt to an N-alkylpiperidine. The third step illustrates the formation of a bicyclic system by the Dieckmann condensation.

Quinuclidone can be reduced to quinuclidine.⁶ Depending on the availability of starting materials, either this reduction or the dehydrative cyclization of 4-(2-hydroxyethyl)piperidine¹⁰ is the most convenient synthesis of quinuclidine.

1. University of Basel, Basel, Switzerland.
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2a-THIOHOMOPHTHALIMIDE

[3(2H)-Isoquinolone, 1,4-dihydro-1-thioxo-]

Submitted by P. A. S. SMITH and R. O. KAN¹

Checked by MELVIN S. NEWMAN and R. L. CHILDERS

1. Procedure

A. *Phenylacetyl isothiocyanate*. Twenty-five grams (0.16 mole) of phenylacetyl chloride (Note 1), 100 ml. of benzene, and 53 g. (0.16 mole) of lead thiocyanate (Note 2) are placed in a 1-l., three-necked, round-bottomed flask equipped with a mechanical stirrer and a reflux condenser. The stirrer is started and the mixture is refluxed for 5 hours. A small amount of activated charcoal is added, and refluxing is continued for 5 minutes. The warm mixture is filtered through a Büchner funnel under suction (Note 3), and the solid on the filter is washed with two 50-ml. portions of benzene. The solvent is removed from the filtrate under reduced pressure, and the residue is distilled at once to yield 17.5–22.7 g. (61–79%) of phenylacetyl isothiocyanate, b.p. 83–91° at about 0.3 mm. It is a colorless liquid that rapidly darkens on standing (Notes 4 and 5).

B. *2a-Thiohomophthalimide*. In a 500-ml., three-necked, round-bottomed flask equipped with a mechanical stirrer, a reflux condenser, and a dropping funnel are placed 150 ml. of carbon disulfide (Note 6) and 29.3 g. (0.22 mole) of anhydrous powdered aluminum chloride. The stirrer is started, and 17.7 g. (0.10 mole)

of phenylacetyl isothiocyanate is added dropwise at such a rate that the solvent refluxes gently. The total addition time is about 5 minutes. The mixture is refluxed gently for 2 hours (Note 7) and is cooled in an ice bath and treated with a solution of 10 ml. of 12*N* hydrochloric acid in 90 ml. of water; the addition is dropwise at first, more rapid later. Stirring is continued at room temperature for another hour. Crude 2*a*-thiohomophthalimide is collected by filtration on a 10-cm. Büchner funnel and is pressed dry and subsequently dried thoroughly, either in a vacuum desiccator or in an oven at 40–45° (*Caution! Note 8*). A solution of the imide in 300 ml. of boiling glacial acetic acid is boiled a few minutes with a small amount of activated charcoal, and the hot solution is filtered through a large fluted filter as rapidly as possible to prevent premature crystallization on the filter. Orange-yellow crystals of 2*a*-homophthalimide precipitate when the filtrate is cooled. They are separated by filtration and dried in an oven or a vacuum desiccator; weight 9.2–13.3 g. (52–75%); m.p. 221–222°.

2. Notes

1. Eastman Kodak Company white label grade of phenylacetyl chloride was used, but equally good results are obtained with the crude acid chloride obtained by treating phenylacetic acid with an excess of thionyl chloride and removing the latter under reduced pressure.

2. Lead thiocyanate was made by stirring together a solution of 45 g. (1.37 moles) of lead nitrate in 360 ml. of boiling water with a solution of 266 g. (2.74 moles) of potassium thiocyanate in 140 ml. of boiling water. The mixture was cooled to room temperature, and 437 g. (99%) of lead thiocyanate was separated by filtration and air-dried.

3. If the filtrate is not clear, filtration should be repeated through the same filter.

4. When large quantities are used, the distillation should be performed in parts, for on prolonged heating phenylacetyl isothiocyanate decomposes with a heavy loss in yield.

5. The distillation should be carried out just before commencing Part B.

6. *sym*-Tetrachloroethane may be substituted for carbon disulfide. In this case 5 minutes of heating on a steam bath, or even no heating at all, gives satisfactory results, although the product is of slightly lower purity. The solvent may be removed quickly by steam distillation of the reaction mixture after addition of dilute acid, and the product is isolated by filtration of the slurry remaining in the flask.

7. The best heating device has been found to be an infrared lamp placed about 20 cm. from the vessel.

8. Drying at higher temperatures can be dangerous because of the low flash-point of carbon disulfide.

3. Methods of Preparation

The only reported method of preparation of 2a-thiohomophthalimide is by the reaction described here.²

4. Merits of the Preparation

This is a general method of converting arylcarbonyl and arylacetyl isothiocyanates to the corresponding thioimides as the following examples show (percent yield and duration of the reaction follow each example): 6-methyl-1a-thiophthalimide² (45%, 4 days); 4,6-dimethyl-1a-thiophthalimide² (64%, 24 hours); 5-methyl-2a-thiohomophthalimide (42%, 4 hours); 4-methyl-2a-thiohomophthalimide (48%, 4 hours); 5-methoxy-2a-thiohomophthalimide (41%, 4 hours); 4-chloro-2-thiohomophthalimide (40%, 4 hours); 1a-phenyl-2a-thiohomophthalimide (40%, 30 minutes); 1a-thio-1,2-naphthalimide² (25%, 4 days); 2a-thio-1-homo-1,2-naphthalimide² (41%, 16 hours); thiophene-2a-thio-2,3-dicarboximide (12%, 24 hours).

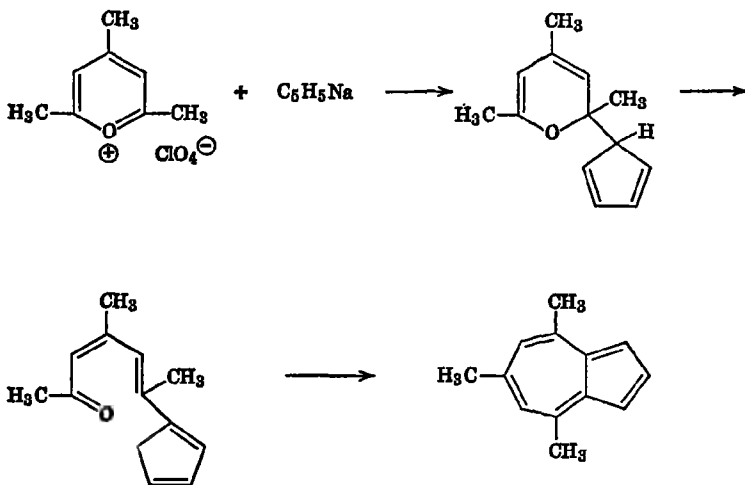
The thioimides can be hydrolyzed to the corresponding dicarboxylic acids.³ The thioimides can be converted to the corresponding imides, and thiohomophthalimides can be converted to phthalimides; both conversions are one-step processes.⁴ Thus a variety of substituted phthalic and homophthalic acids and their derivatives are available from these thioimides.

Thiohomophthalimides can be reduced to tetrahydroisoquinolines.²

1. Department of Chemistry, University of Michigan, Ann Arbor, Michigan.
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4,6,8-TRIMETHYLAZULENE

(Azulene, 4,6,8-trimethyl-)



Submitted by K. HAFNER and H. KAISER¹

Checked by KARL BANGERT and VIRGIL BOEKELHEIDE

1. Procedure

A. Cyclopentadienylsodium. A 1-l. four-necked flask (or a three-necked flask with a Y-tube connection) is outfitted with a Trubore[®] stirrer, a pressure-equalizing dropping funnel, a thermometer reaching to the bottom of the flask, and a reflux condenser in whose outlet is placed a T-tube, one side of which leads to a bubble counter and the other is connected to a source of pure

nitrogen. The system is flushed with nitrogen, and a suspension of 23 g. (1.0 mole) of sodium in 350 ml. of dry tetrahydrofuran (Notes 1 and 2) is prepared in the flask. There is then added dropwise with stirring 73.0 g. (1.1 moles) of freshly distilled cyclopentadiene (Note 3). As the exothermic reaction begins, evolution of hydrogen through the bubble counter can be observed immediately. The temperature of the reaction mixture should be kept below 35–40° by intermittent cooling of the flask with an ice bath. At the end of the reaction the color of the solution should be a pale rose; exposure to air causes a rapid change in color to dark brown (Note 4).

B. *4,6,8-Trimethylazulene. Caution! 2,4,6-Trimethylpyrylium perchlorate is explosive. Operations with it should be conducted behind a shield.* The arrangements of the reaction flask used in the preparation of cyclopentadienylsodium are now altered for the next step. While increasing the nitrogen flow rate strongly, the dropping funnel is removed and replaced by a wide-mouthed powder funnel. The strong flow of pure nitrogen coming out of the flask and around the powder funnel prevents the atmosphere from diffusing into the flask to any appreciable extent. Then, with strong stirring of the reaction mixture, 142 g. (0.64 mole) of 2,4,6-trimethylpyrylium perchlorate (*Caution! Moistened with dry tetrahydrofuran, Note 5*) is added in small portions through the powder funnel at such a rate that the immediate exothermic reaction which ensues maintains the temperature of the reaction mixture between 42° and, at most, 48°. The color of the reaction mixture turns purple immediately on addition of the 2,4,6-trimethylpyrylium perchlorate. Usually the addition requires about 1 hour; then the reaction mixture is stirred for an additional 20 minutes. The powder funnel is replaced with a stopper, the condenser is turned downward for distillation, and about 130 ml. of tetrahydrofuran is removed by distillation while stirring is continued. For the distillation the flask is heated on a steam bath, and the temperature of the reaction mixture at the end of the distillation is about 68–70°. The color of the distillate is a weak violet owing to the co-distillation of a small amount of 4,6,8-trimethylazulene. After the reaction mixture has cooled, it is transferred to a 3-l. separatory funnel and diluted, first with

75 ml. of methanol and then with 1 l. of water. This causes the separation of a dark violet oil which is taken up in 400 ml. of petroleum ether (b.p. 60–70°) and separated from the aqueous phase. The aqueous layer is extracted again with 200 ml. of fresh petroleum ether, and the combined petroleum ether extracts are washed five times with 175-ml. portions of water. Since a small quantity of a greasy by-product separates at the interface during the washing with water, the petroleum ether extract, after the final washing, is purified by passing it through a Büchner funnel lined with asbestos fibers as a filtering aid. After the filtrate has been dried over calcium chloride, the solution is concentrated under reduced pressure, and the residue is carefully freed of solvent by heating on a steam bath under reduced pressure for 4 hours.

The crude product is then transferred to an apparatus suitable for distillation of solids (Note 6), and this is joined to a high-vacuum system capable of a vacuum in the range of 10^{-5} mm. Distillation begins when the bath temperature reaches about 190°; a boiling point of around 120° is usually observed. When the distillate first begins to appear brown rather than violet, the distillation is stopped immediately (Note 7). The crystalline distillate (ca. 70 g.) is dissolved in 20 ml. of hot ethanol, filtered while hot, and allowed to cool. The solid (about 60 g. of crystals, m.p. 74–76°) is recrystallized from 20 ml. of ethanol to yield 47–53 g. (43–49%) of 4,6,8-trimethylazulene as dark-violet plates, m.p. 80–81° (Note 8).

2. Notes

1. The suspension of sodium is best prepared as follows. In a three-necked flask fitted with a ground-glass stopper, a reflux condenser, and a Vibromischer (available from A. G. für Chemie-Apparatebau, Zurich, Switzerland) are placed 150 ml. of toluene and 23 g. of sodium. When the toluene is boiling under reflux, the melted sodium is dispersed by the Vibromischer, and the flask is quickly cooled. Under nitrogen atmosphere the toluene is removed by decantation and is replaced by 350 ml. of dry tetrahydrofuran.

2. The dry tetrahydrofuran can be prepared by allowing tetrahydrofuran to stand over sodium, decanting, and distilling from lithium aluminum hydride.

3. For the preparation of cyclopentadiene from its dimer, see M. Korach, D. R. Nielsen, and W. H. Rideout, *Org. Syntheses*, **42**, 50 (1962).

4. If desired, the cyclopentadienylsodium concentration in solution can be determined by withdrawing 1 ml. of solution, diluting this with 100 ml. of water, and titrating the resulting aqueous sodium hydroxide solution with 0.1*N* hydrochloric acid using methyl red as an indicator.

5. The 2,4,6-trimethylpyrylium perchlorate, obtained and stored as described by Balaban and Nenitzescu² or by Hafner and Kaiser,³ is used directly.

6. A round-bottomed, standard-taper flask with a Claisen head carrying an ebullition capillary and a thermometer and attached to a two-necked flask with one neck for vacuum takeoff is satisfactory. It is important that the setup allow for heating by either flame or infrared lamp to melt the solid distillate and prevent its clogging the vapor passage.

7. It is helpful to empty the brown tarry residue from the distillation flask while it is still hot. The flask can then be cleaned by using a sulfuric acid-chromic acid solution.

8. For purification of small amounts of 4,6,8-trimethylazulene it is advantageous to dissolve it in a small amount of methanol and treat the solution with activated carbon.

3. Methods of Preparation

This procedure is adapted from that described earlier by Hafner and Kaiser,⁴ and apparently it is the only method that has been used for synthesizing 4,6,8-trimethylazulene.

4. Merits of the Preparation

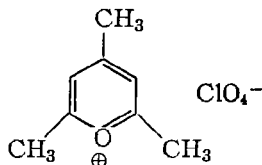
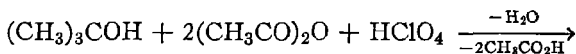
This procedure illustrates a simple and general method for preparing azulenes. It is far more convenient and proceeds in much better yield than previous syntheses of azulenes involving

dehydrogenation.⁵ Also, it is superior to the alternative methods utilizing the monoanil of glutacondialdehyde⁶ or pyridinium salts.^{7,8} In fact, this procedure has made the azulenes a readily available class of compounds for study and use as starting materials. Illustrative of the latter are the recent syntheses of pentalene,⁹ heptalene,⁹ and *peri*-benzazulene derivatives.¹⁰

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2,4,6-TRIMETHYLPYRYLIUM PERCHLORATE

Method I



Submitted by A. T. BALABAN¹ and C. D. NENITZESCU²
 Checked by KARL BANGERT and VIRGIL BOERELHEIDE

1. Procedure

Caution! 2,4,6-Trimethylpyrylium perchlorate is explosive. Operations should be conducted behind a shield, and directions should be followed closely (see Note 1 of Method I and Section 4 before carrying out these preparations).

In a 2-l. four-necked flask (or a three-necked flask with a

Y-tube connection) outfitted with a stirrer, a short reflux condenser, a dropping funnel, and a thermometer reaching to the bottom of the flask, 148 g. (2.0 moles) of anhydrous *t*-butyl alcohol and 1020 g. (945 ml., 10.0 moles) of acetic anhydride are mixed with stirring and cooled to -10° by means of an ice-salt cooling bath. Then 250 g. (150 ml., 1.75 moles) of 70% perchloric acid is added rapidly from the dropping funnel to the stirred mixture over a period of 5–7 minutes (Note 2). With the first few drops a vigorous reaction begins which is manifested by evolution of fumes, coloration of the reaction mixture to orange and then reddish brown, and a rapid rise in temperature. When the temperature of the reaction mixture reaches 40 – 50° , crystals of 2,4,6-trimethylpyrylium perchlorate should begin to separate (Note 3); then the temperature is allowed to rise to 100° . The rate of perchloric acid introduction and the use of the cooling bath are then so controlled that the temperature of the reaction mixture is maintained between 100° and 105° . Toward the end of the addition the perchloric acid may be added quite rapidly and the desired temperature may still be maintained. After all the perchloric acid has been added, the cooling bath is removed and stirring of the mixture is continued. The temperature remains at about 90° for 10 or 15 minutes and then falls to about 75° after 30 minutes. The dark-brown stirred mixture is cooled once again until the temperature has fallen to 15° . The crystalline 2,4,6-trimethylpyrylium perchlorate, which has separated, is collected on a Büchner funnel and is washed on the funnel with a 1:1 mixture of acetic acid and ether and then washed twice with ether (Note 4). Suction is stopped before the crystals are dry. The product can be air-dried to give 195–210 g. (50–54%) of yellow crystals, m.p. 244° dec. (Notes 1, 5, and 6). For storing or for use in the preparation of 4,6,8-trimethylazulene, however, it is best to place the product in a cork-stoppered flask and moisten it with dry tetrahydrofuran.

2. Notes

1. The impact sensitivity of 2,4,6-trimethylpyrylium perchlorate was examined by Dr. T. E. Stevens at the Redstone Arsenal

Division of Rohm and Haas Co., and the compound was found to be slightly more sensitive to detonation by impact than the commercial explosive RDX. This point should be kept constantly in mind. When the crystals are handled as a slurry or are wet with solvent, the hazard is considerably reduced. On the other hand, the dry perchlorate should be handled with great care and should never be crushed, rubbed, or pushed through a narrow opening.

2. The specified order of mixing the three reagents is critical. If the reagent added to the solution of the other two is *t*-butyl alcohol or acetic anhydride, large amounts of triisobutylenes are formed, separating as a colorless upper layer.

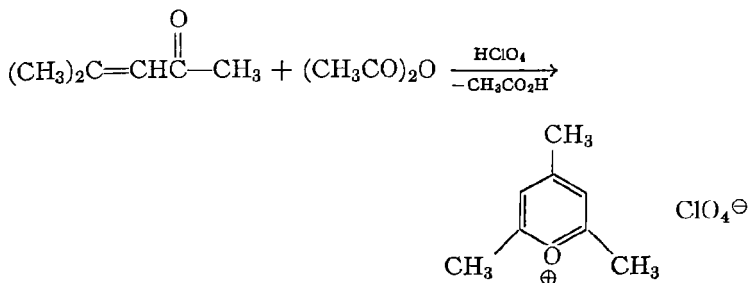
3. The rate of perchloric acid introduction should be slow at first so that in the range of 40–50° crystals of the 2,4,6-trimethylpyrylium perchlorate will begin to appear. Then the rate of addition should be increased to maintain the temperature in the optimum range of 100–105°. If the temperature rises too rapidly, no crystals will appear and the yield will be somewhat lower. Then seeding is helpful.

4. If crystallization is not complete, dilution of the filtrate by the ether washings will cause separation of additional crystals. These are collected separately because they are finer and less pure. Concentration of filtrates is to be avoided because severe explosions³ have been reported when solutions of perchloric acid in acetic acid were concentrated.

5. The product is of satisfactory purity for use in the 4,6,8-trimethylazulene preparation without further purification. Recrystallization of a small sample of the 2,4,6-trimethylpyrylium perchlorate from a seven-fold amount of hot water, containing a few drops of perchloric acid and some carbon black, gives colorless crystals, m.p. 245–247° dec. However, the recrystallization of larger amounts in this way presents some hazard and is not recommended. Concentration of filtrates should be avoided (see Note 4).

6. The preparation of 2,4,6-trimethylpyrylium perchlorate may be carried out on a much smaller scale, such as one-tenth, with only a small lowering of the yield.

Method II

Submitted by K. HAFNER and H. KAISER ⁴

Checked by VIRGIL BOEKELHEIDE and H. FLEISCHER

1. Procedure

Caution! 2,4,6-Trimethylpyrylium perchlorate is explosive. Operations should be conducted behind a shield, and directions should be followed closely (see Note 1 of Method I and Section 4 before carrying out these preparations).

In a 2-l. four-necked flask (or a three-necked flask with a Y-tube connector) equipped with a stirrer, a reflux condenser, a dropping funnel, and a thermometer extending nearly to the bottom of the flask is placed 550 ml. (595 g., 5.83 moles) of acetic anhydride which is cooled to 0° with an ice-salt bath. Then 180 ml. (300 g., 2.09 moles) of a 70% solution of perchloric acid is added with stirring at a rate such that the temperature does not rise above 8° (Note 1). This step takes about 3 hours. The mixture is continually cooled and stirred, and 240 ml. (204 g., 2.09 moles) of mesityl oxide is then added slowly. The slow addition of 370 ml. (400 g., 3.92 moles) of acetic anhydride follows. The ice bath is then replaced by a water bath; the temperature of the reaction mixture will usually rise to 50–70° because of the heat liberated by the exothermic reaction, and the reaction mixture will turn dark. The reaction mixture is heated on a steam bath for 15 minutes to complete the reaction, and the mixture is then allowed to cool and stand at room temperature for 2 hours. The crystals,

which have separated from the brown solution, are collected on a Büchner funnel and are washed on the funnel twice with 100-ml. portions of acetic acid, twice with 100-ml. portions of absolute ethanol, and twice with 100-ml. portions of absolute ether. This gives 250–260 g. (54–56%) of pale-yellow to light-brown crystals, m.p. 240° dec. (Note 2). For storage the crystals should be transferred, without drying, to an ordinary flask, moistened with dry tetrahydrofuran, and then kept in this state by stoppering the flask with an ordinary cork (Note 3).

2. Notes

1. Since the reaction is quite exothermic, the mixture must be well stirred to avoid developing any local hot spots which could lead to explosions. Although no difficulties were encountered in either the submitters' or checkers' laboratories, it is well to keep in mind that 2,4,6-trimethylpyrylium perchlorate is potentially hazardous; hence due precaution should be exercised at all times.

2. Although a small sample of 2,4,6-trimethylpyrylium perchlorate may with care be recrystallized from acetic acid to give white crystals, m.p. 245–247° dec., it is recommended that this not be done with larger quantities. The 2,4,6-trimethylpyrylium perchlorate is of satisfactory purity for use in the 4,6,8-trimethylazulene preparation without further purification.

3. The hazard of handling 2,4,6-trimethylpyrylium perchlorate is greatly reduced if the crystals are kept moist with a solvent such as tetrahydrofuran. The flask used for storage should be stoppered with a cork rather than a ground-glass stopper to avoid the possibility of initiating an explosion by the grinding action of the stopper.

3. Methods of Preparation

2,4,6-Trimethylpyrylium perchlorate has been prepared from 2,6-dimethylpyrone and methylmagnesium halides;⁵ from mesityl oxide and sulfoacetic acid;⁶ from mesityl oxide (or less satisfactorily from acetone) and a mixture of acetic anhydride and perchloric acid;⁷ from mesityl oxide, acetyl chloride, and aluminum chloride;⁸ and from *t*-butyl chloride, acetyl chloride,

and aluminum chloride.⁸ The procedure given under Method I is adapted from that reported by Balaban and Nenitzescu⁹ and is similar to that of Praill and Whitear.¹⁰ The procedure given under II is adapted from that reported by Hafner and Kaiser.¹¹

4. Merits of the Preparation

2,4,6-Trimethylpyrylium perchlorate is a very versatile and useful starting material. Thus its reaction with cyclopentadienylsodium has made 4,6,8-trimethylazulene¹² easily available for general studies of the properties of azulenes¹³ and for the synthesis of related compounds.¹⁴ In addition, pyrylium salts are readily converted to a variety of pyridine derivatives^{9,15} as well as to derivatives of nitrobenzene¹⁶ and phenol.^{9,17,18} It is clear that its value as a starting material is such that it is receiving wide use.

In including this preparation in *Organic Syntheses*, it was felt that standard procedures which have been tested in more than one laboratory without difficulty and which attempt to point out as clearly as possible the potential hazards involved would serve a useful function for those who, despite the hazards, find this a necessary and important starting material.

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SUBJECT INDEX

(This index comprises material from Volumes 40-44 only; for previous volumes see Collective Volumes 1, 2, 3, and 4).

Names in small capital letters refer to the titles of individual preparations. A number in ordinary boldface type denotes the volume. A page number in boldface italics indicates that the detailed preparative directions are given or referred to; entries so treated include principal products and major by-products, special reagents or intermediates (which may or may not be isolated), compounds mentioned in the text or Notes as having been prepared by the method given, and apparatus described in detail or illustrated by a figure. Page numbers in ordinary type indicate pages on which a compound or subject is mentioned in connection with other preparations.

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the current style sheet may be obtained from the Secretary of the Editorial Board. In Section 3, **Methods of Preparation**, there should be described other practical methods for preparing the compound which have appeared in the literature. It is unnecessary to mention methods which have been published but are of no practical synthetic value. In Section 4, **Merits of the Preparation**, a statement should be made indicating why the preparation is published in *Organic Syntheses*. Among the obvious reasons for publication would be the novelty of the procedure, general scope of the synthetic method, specific interest in the compound or its use as an intermediate for preparing other compounds, convenience of the method, and improvement in yields. Two copies of each procedure should be submitted to the Secretary of the Editorial Board. It is sometimes helpful to the Board if there is an accompanying letter setting forth the features of the preparation which are of interest.

Additions, corrections, and improvements to the preparations previously published are welcomed and should be directed to the Secretary.

EDITOR'S PREFACE

The preparations presented in this volume of *Organic Syntheses* were selected from those manuscripts submitted voluntarily, and those received in response to the solicitation program. The choices reflect the continuing policy by the editors of presenting examples which illustrate new or general methods of organic synthesis, significant improvements in older methods of synthesis, and the preparation of compounds of wide general interest.

This volume contains a relatively large number of preparations which illustrate new or general methods, including: a method for carboxylating saturated hydrocarbons containing a tertiary hydrogen (1-adamantanecarboxylic acid); a general method for the synthesis of aldehydes (*o*-anisaldehyde); a method for the conversion of carbonyl groups to difluoromethylene groups (α,α -difluorotoluene); a method for the conversion of 2,6-dialkylphenols to 1,3-dihydro-2H-azepin-2-ones (1,3-dihydro-3,5,7-trimethyl-2H-azepin-2-one); a method for the conversion of olefins and *t*-alcohols to *t*-amines by the Ritter reaction (α,α -dimethyl- β -phenethylamine); a general method for the synthesis of ketimines (diphenyl ketimine); the use of lithio-esters for the preparation of β -hydroxy esters (ethyl β -hydroxy- β,β -diphenylpropionate); a method for the synthesis of N-alkylallenimines by ring closure of N-(2-bromoallyl)-alkylamines by action of sodium amide; the use of ethylene bromide as an entrainment agent in Grignard syntheses (pentachlorobenzoic acid); a method for the synthesis of azulenes (4,6,8-trimethylazulene); and the Decker reaction for the preparation of N-methylalkylamines (N-methylbutylamine and N-methylethylamine).

Certain preparations—mesitoic acid, 7-*t*-butoxynorbornadiene, cyclopentanecarboxaldehyde, *t*-butyl azidoformate, indole-

3-acetic acid, 2,3-diaminopyridine, and 2,4,6-trimethylpyrylium perchlorate—illustrate new or improved methods for the synthesis of compounds of wide general interest. In including the preparation of 2,4,6-trimethylpyrylium perchlorate, it was felt that standard procedures which have been tested in more than one laboratory without difficulty and which attempt to point out as clearly as possible the potential hazards involved would serve a useful function for those who, despite the hazards, find this a necessary and important starting material.

The editors express their appreciation to chemists in this country and throughout the world for their contributions to this series, as reflected by the high quality of the preparations received through the voluntary submission program. The editors will welcome recommendations by readers of *Organic Syntheses* of preparations to be included in subsequent volumes. For this purpose, submission of a brief description of the reaction and the merits of the preparation will permit preliminary evaluation by the members of the Board of Editors.

WILLIAM E. PARHAM

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